Role of ultrasound Acoustic Radiation Force Impulse in differentiating benign and malignant solid breast masses

A dissertation submitted in partial fulfilment of MD Radiodiagnosis (Branch VIII) examination of the Tamil Nadu Dr. M.G.R Medical University, Chennai to be held in April 2015

CERTIFICATE

This is to certify that the dissertation entitled "Role of ultrasound Acoustic Radiation Force Impulse in differentiating benign and malignant solid breast masses" is the bonafide original work of Dr. Vitsizono Sakhrie submitted in partial fulfilment of the requirement for MD Radiodiagnosis (Branch VIII) Degree Examination of the Tamil Nadu Dr. M.G.R Medical University, Chennai to be held in April 2015.

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DECLARATION

I, Dr. Vitsizono Sakhrie, hereby declare that this dissertation entitled "Role of ultrasound Acoustic Radiation Force Impulse in differentiating benign and malignant solid breast masses" is an original work done by me in partial fulfilment of the requirement for M.D Radio Diagnosis (Branch- VIII) Degree Examination of The Tamil Nadu Dr M.G.R Medical University, Chennai to be conducted in April, 2015.

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Most importantly, this dissertation is a product of the faith laid on us by all the patients who gave consent to take part in this study.

This dissertation is dedicated to my husband, without whose endless encouragement and support, this would not have become a reality.

Contents

ABSTRACT

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'Role of ultrasound Acoustic Radiation Force Impulse in differentiating benign and malignant solid breast masses'

DEPARTMENT: Radiodiagnosis

NAME OF CANDIDATE: Vitsizono Sakhrie

DEGREE AND SUBJECT: M.D Radiodiagnosis

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OBJECTIVES: The purpose of this study was to identify the role of virtual touch quantification (VTQ) and Virtual touch imaging (VTI) of ARFI elastography in differentiating benign and malignant lesions in patients with solid breast lesions, using histopathological diagnosis as reference standard. The variables evaluated in this study included Shear wave velocity (SWV) of the lesion and surrounding normal tissue along with the SWV velocity ratio using VTQ, VTI elasticity scores using a 5 point scoring system and Area Ratio (AR) of lesion on VTI and B-mode using VTI. We also compared the performance of ARFI (VTI and VTQ) alone and in combination with B-mode USG with that of conventional B mode ultrasonography in the prediction of malignancy in solid breast masses.

METHODS: ARFI was performed in 184 solid breast lesions from 124 patients. Out of the total, 130 lesions had histopathological diagnosis and were included in the final analysis. In this study, following assessment and categorization using BIRADS lexicon by B-mode ultrasound, VTI was performed and calculation of Area Ratios (B-mode/VTI) and elasticity scores based on a 5 point scoring system was made. Shear Wave Velocity (SWV) measurement by VTQ was also performed within the lesion and surrounding tissue, and SWV ratios calculated from these two values.

Statistical analysis was performed using SPSS software version 16. The descriptive data were expressed in mean ± standard deviation. Student's t-test was used for comparing mean SWV values, SWV ratios and area ratios. Receiver operating characteristic (ROC) curves were drawn to compare the diagnostic performance of B-mode ultrasound, VTI, VTQ and combined VTI + VTQ. P values < 0.05 was taken as statistically significant.

RESULTS: The elasticity scores and mean Area Ratio of benign lesions were significantly different from that of the malignant lesions (mean AR of 1.33±0.82 for benign lesions vs 0.38±0.49 for malignant lesions, p value <0.001). The mean SWV between the benign and malignant lesions also showed significant difference (3.08 ± 1.99 m/s for benign and 8.43± 1.75m/s for malignant group, p value <0.001). The optimal cut-off values in predicting malignancy obtained from the Receiver Operating Curve analysis were 1.41 for Area Ratio and 5.55m/s for SWV. Combined criteria using B-mode USG BIRADS lexicon and VTI elasticity score had the best diagnostic performance, the performance being superior to the use of B-mode USG BIRADS and VTI alone.

We conclude that the combination of ARFI with conventional B-mode ultrasound can improve the specificity of the diagnostic test and potentially reduce the number of invasive biopsies in indeterminate breast lesions.

KEYWORDS: Acoustic Radiation Force Impulse (ARFI), Virtual Touch Imaging (VTI), Virtual Touch Quantification (VTQ), solid breast lesions.

INTRODUCTION

At present, mammography and B-mode ultrasound are the two main imaging modalities routinely used for characterization of breast lesions. The current practice of lesion characterization with conventional B-mode imaging based on the ACR BIRADS lexicon (4^{th} edition) has resulted in standardization of breast reporting however there are still situations where lesions are indeterminate, thereby subjecting many of these indeterminate lesions to an invasive biopsy.

A technique which would increase the characterization of a breast lesion and improve the specificity of diagnosis is therefore highly desirable to avoid unnecessary biopsies. Elastography is a recently introduced technology which provides information on tissue stiffness. It is based on the observation that malignant tissue is stiffer compared to normal tissue. There are several elastography techniques depending on how the tissue compression is applied. ARFI is a fairly new technique which does not require the operator to apply pressure, hence it is more objective and reproducible compared to freehand strain elastography.

Several studies have shown that ARFI elastography is a promising tool in breast lesion characterization with a potential to ultimately reduce the biopsy rates in indeterminate or benign lesions.

In this study, we have looked into the role of ARFI elastography using VTI and VTQ in differentiating benign and malignant lesions. Our study is based on the hypothesis that ARFI can reliably predict malignancy in solid breast lesions based on the parameters which reflect tissue stiffness. For this purpose, qualitative assessment by means of elasticity scores using VTI mode was done while quantitative assessment by means of Area Ratio of lesions on conventional B-mode USG and virtual touch imaging, shear-wave velocity measurements from within the lesion and surrounding tissue, calculation of shear wave velocity ratios between lesion and surrounding normal tissue were made. Also, the performance of combined VTI and VTQ imaging of ARFI elastography was compared with conventional B mode sonography as well as its individual (VTI alone and VTQ alone) performance as compared to B mode sonography using histopathology as the reference standard.

AIM

To assess the role of Acoustic radiation force impulse (ARFI) elastography in differentiating benign and malignant lesions in patients with solid breast lesions, using histopathological diagnosis as reference standard.

OBJECTIVES

1) To identify the role of virtual touch quantification (VTQ) and Virtual touch imaging (VTI) of ARFI elastography in differentiating benign and malignant lesions in patients with solid breast lesions, using histopathological diagnosis as reference standard.

The variables studied include:

- Shear wave velocity of the lesion and surrounding normal tissue using VTQ.
- Shear wave velocity ratio between lesion and surrounding tissue using VTQ.
- Area Ratio (AR) of lesion on VTI and B-mode using Virtual Touch Imaging.
- Elasticity scoring based on a visual 5 point system using Virtual Touch Imaging.

2) To compare the performance of ARFI (VTI and VTQ) with that of conventional B mode ultrasonography in the prediction of malignancy in solid breast masses.

3) To compare the performance of combined B mode USG with VTI and VTQ with that of conventional B mode alone in the prediction of malignancy in solid breast masses.

REVIEW OF LITERATURE

NORMAL BREAST ANATOMY:

The breast is made up of three main structures: skin, subcutaneous tissue and breast parenchyma. Breast tissue is composed of both epithelial and stromal elements, the epithelial component comprises of the branching ducts which connects the structural and functional units of the breast (the lobules) to the nipple. The stroma is composed of adipose and fibrous connective tissue, forming the majority of the breast volume.

Figure 1: Normal breast anatomy.

A - pectoralis major

B - pectoralis minor

C - breast lobule

D - Cooper's ligaments

E – fatty tissue

F – lactiferous ducts

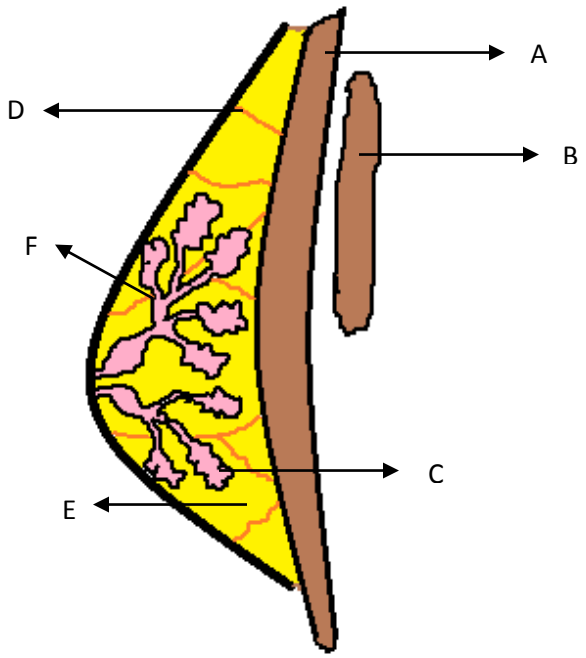


Figure: 1 – Schematic diagram showing the normal breast anatomy.

The breast is enclosed by the superficial pectoral fascia which is continuous with the superficial abdominal fascia. The breast is anterior to the deep pectoral fascia which covers pectoralis major and serratus anterior muscles. The suspensory ligaments of Cooper are fibrous bands connecting these two fascial layers (1).

Blood supply and lymphatic drainage:

The main blood supply to the breast is from the internal mammary artery. Approximately one-third of the blood supply is provided by the lateral thoracic arteries.

The lymphatic drainage is comprised of a superficial (subepithelial and subdermal) and a deep system, the direction of lymph flow is from superficial to deep. Lymph flow from the deep system is towards the axillary, internal mammary and clavicular nodes.

To describe metastatic nodal involvement in breast cancer, axillary nodes are grouped by anatomic location, dividing them into arbitrary levels. Level I nodes are lateral to the lateral border of the pectoralis minor muscle, level II nodes are posterior to the pectoralis minor muscle, and level III nodes are medial to the medial border of the pectoralis minor muscle. The internal mammary nodes are found in the extrapleural fat of the intercostal spaces along the internal mammary vessels. These nodes also receive lymph from all the quadrants of the breast.

BREAST CANCER - PATHOLOGY

Gross and microscopic features:

Breast cancer comprises of a wide group of microscopically distinct lesions with different behavioural patterns. Breast carcinomas are broadly classified into in-situ carcinomas and invasive carcinomas. In-situ carcinomas are either ductal or lobular, while invasive carcinomas are divided into several subtypes such as (2):

1. Invasive ductal 76%
2. Invasive lobular 8%
3. Ductal / lobular 7%
4. Mucinous 2.4%
5. Tubular 1.5%
6. Medullary 1.2%
7. Papillary 1%
8. Others <5%

On macroscopic examination, infiltrating ductal carcinomas are hard masses infiltrating the surrounding tissue to form irregular spiculated masses, the intense fibrous reaction induced by the malignant cells in the surrounding tissue is what gives rise to the clinically palpable masses, seen as radiographic densities on mammography and solid characteristics on sonography.

Infiltrating lobular carcinomas are frequently bilateral and multicentric, tends to metastasize later and seen more commonly in older age group (3). Mucinous carcinomas are ill-defined or lobulated soft tumours with a gelatinous appearance on gross pathology (4). Medullary carcinomas are well-defined tumours with internal hemorrhagic and necrotic areas.

Among the different types, lobular and ductal / lobular carcinomas are known to be diagnosed at an advanced stage as compared to the medullary, tubular and mucinous subtypes. Less aggressive behaviour is observed in mucinous, tubular and papillary carcinomas (2).

Hormone receptor status:

The content of ER and PR in the lobular structures of the breast is directly proportional to the rate of cellular proliferation.

The subtypes of breast carcinoma which are more likely to be ER/PR negative and high grade includes medullary, comedo and inflammatory carcinomas, while lobular, ductal / lobular, mucinous, tubular and papillary carcinomas are less likely to be ER/PR negative (2). ER/PR negative tumours have lower response to endocrine therapy with upto 77% response rates seen in ER/PR positive tumours (5).

Human Epidermal Growth factor Receptor2 (HER2):

The HER2 gene is overexpressed in upto 20% of breast cancers and it is associated with worse prognosis in terms of higher recurrence and mortality rates. It plays an important role in clinical decision making regarding the need for adjuvant systemic chemotherapy. HER2 status is associated with either resistance or sensitivity to chemotherapeutic and hormonal therapies. HER2 targeting agents improve survival in metastatic disease (6).

The American Society of Clinical Oncology / College of American pathologists' guideline recommends determination of HER2 status of all newly diagnosed invasive cancer. This panel recommends an algorithm to define positive, equivocal and negative results for HER2 expression. A positive result being Immunohistochemistry staining of 3 + (uniform and intense staining of 30% of tumour cells), a fluorescent-in-situ hybridization result of >6 HER2 gene copies per nucleus, FISH ratio of more than 2.2; a negative result being IHC staining of 0 or 1+, FISH result of <4 HER2 gene copies per nucleus and a FISH ratio of <1.8 (6).

Triple-negative breast cancer in Indian population:

Absence of estrogen receptor (ER), progesterone receptor (PR) and Human epidermal growth factor receptor (HER2NEU) is known as triple negative breast cancer and it is associated with

poor prognosis. (7) Studies amongst Indian population have shown a pattern of earlier occurrence with more aggressive behavior in triple negative tumours (7,8).

EPIDEMIOLOGY OF BREAST CANCER

Incidence:

Globally, carcinoma breast is the second most common cancer after lung cancer (1.4 million cases, 10.9%). It is considered the most common cancer in women constituting about 22% of all cancers, with an estimate of over 1 million new cases every year (9).

In India, breast cancer is the second most common cancer after cervical cancer with about 75,000 new cases every year. Studies have shown that Indian women have aggressive breast cancer with a higher incidence of ER/PR negative and HER2NEU positive status (10).

Age:

The most commonly affected age group includes the 4^{th} and 5^{th} decades, with younger age being affected in patients with genetic predisposition (11).

Risk factors:

Multiple risk factors have been identified in the pathogenesis of breast cancer, some of which are summarized below (12)

1. Increasing age
2. Female gender
3. Obesity
4. Hormonal influence – high estrogen levels, exogenous HRT
5. Breast pathology – benign breast disease
6. Reproductive factors – early menarche or late menopause, nulliparous, late age pregnancy
7. Positive personal or family history, inherited genetic risk factors
8. Others: demographic factors like race and geographic location, lifestyle factors like alcohol and smoking, environmental factors like exposure to ionizing radiations

Prognosis

An improvement in imaging together with increased awareness of breast cancer has resulted in early detection of the disease, thereby improving the overall survival of the patient (11). Prognostic factors include age (<35 and >65 years), race, tumour stage, hormone receptor expression and HER2 overexpression. Hormone receptor status and HER2 overexpression are the most important predictors of treatment response to systemic therapy (13).

According to TNM staging, the survival rates range from 95% for stage I disease to 18% for stage IV disease.

CURRENT MANAGEMENT STRATEGY IN BREAST CANCER

Management of breast cancer involves a multidisciplinary team comprising of surgical, radiation and medical oncology (13).

Treatment approach is based on the stage at presentation. Clinical staging is based on the AJCC (American Joint Committee on Cancer) guidelines using the TNM (Tumour Node Metastasis) classification (Annexure --). For the purpose of treatment planning, breast cancer is grouped into:

Early stage – stage 1, IIA and a subset of IIB (T2N1)

Locally advanced - subset of IIB (T3N0) and stage IIIA to IIIC

Early stage disease is treated with primary surgery of the breast (lumpectomy or mastectomy) and nodes with or without RT. Adjuvant systemic chemotherapy is decided based on the tumour characteristics such as hormone receptor status and HER2 status.

Locally advanced disease is managed with a multimodality approach in the form of neoadjuvant systemic therapy followed by locoregional surgery. Further treatment with adjuvant therapy is based on tumour characteristics and patient's clinical status.

ROLE OF SCREENING – CURRENT RECOMMENDATIONS

The goal of screening is to provide primary and secondary prevention of disease. The early detection of cancer has direct impact on patient survival rates, decreasing the mortality by prompt initiation of appropriate treatment.

The efficacy of breast self-examination (BSE) is not proven. It is currently recommended as an adjunct to mammography and clinical breast examination (CBE). Clinical breast examination is recommended by the American Cancer Society (ACS) every 3 years from age 20 - 39 and annually thereafter (14).

The 2013 NCCN (National Comprehensive Cancer Network) guidelines recommend annual CBE and annual mammography for women with no increased risk for breast cancer to start at 40 years along with BSE for creating self-awareness. For patients with increased risk, it recommends annual CBE, annual mammography starting at 35 years, breast awareness and annual MRI (15).

The latest breast cancer screening guidelines recommended by the American Cancer Society includes an overlapping approach by using dual modalities for screening in high-risk patients.

According to the 2007 ACS guidelines, annual breast MRI along with mammography is recommended for patients with 20-25% lifetime risk, including patients with certain risk factors like BRCA, first degree relative with breast cancer etc. It does not recommend screening MRI in patients with low risk (<15%) (16)

ROLE OF IMAGING IN DIAGNOSIS OF BREAST CANCER

There has been considerable advancement in the field of breast imaging with some of the new techniques aimed at improving lesion detection while others are intended for better characterization of breast lesions. Examples of the former include Computer Aided Detection and Full Field Digital Mammography, while Magnetic Resonance Imaging and Sonoelastography are modalities aimed at improving lesion characterization and increasing the specificity of the diagnostic tool.

A multimodality approach continues to be required in the diagnosis and characterization of breast lesions and no single imaging modality can be considered as a standalone diagnostic technique in the work up of breast abnormalities (11).

Conventional modalities:

Apart from clinical palpation, the commonly used modalities for assessment of breast masses and determination of their malignant risk include mammography and B-mode ultrasound. However,

histopathology obtained by percutaneous or open surgical biopsy remains the confirmatory test for establishing the nature of breast masses (17).

A continuing challenge in clinical practice is the non-invasive diagnosis of breast cancer. Although mammography and sonography has shown high sensitivities in the diagnosis of breast cancer, there is still overlap in the features between benign and malignant lesions resulting in high rates of invasive procedures like biopsies. It has been observed that upto 70-90% of breast biopsies are performed for benign lesions. This is accompanied by undue patient anxiety and increased cost incurred by the patient (18)

These limitations of existing diagnostic modalities have raised a need for newer technology which can complement the existing ones and improve diagnostic accuracies, thereby decreasing the number of unnecessary biopsies.

THE ULTRASOUND BIRADS LEXICON:

Before the introduction of the Breast Imaging Reporting and Data System (BIRADS) by the American College of Radiology, there was considerable variability in the terms used in the reporting of mammograms which resulted in confusion among the treating physicians. The current practice of reporting breast lesions using the BIRADS lexicon was first started in 1993 with the aim to standardize mammography reporting and improve communication between clinicians (19). Since its inception, three editions have been made in the BIRADS lexicon, latest

being the 2003 version where in addition to the mammographic descriptors, ultrasound BIRADS descriptors were also introduced (20).

Sonographic BIRADS descriptors (4th edition):

Orientation	Parallel Not parallel
Shape	Oval Round Irregular
Lesion boundary	Abrupt interface Echogenic halo
Echo pattern	Anechoic Hyperechoic Complex Hypoechoic Isoechoic
Posterior acoustic features	None Enhancement Shadowing Combined

Surrounding tissues	Duct changes Cooper ligament changes Edema Architectural distortion Skin thickening Skin retraction
Calcification	Macrocalcification Microcalcification in mass Microcalcification out of mass
Special cases	Clustered microcysts Complicated cysts Mass in skin Foreign body Intramammary node Axillary node
Vascularity	Not present or not assessed Present in lesion Present adjacent to lesion Diffusely increased in adjacent tissue

BIRADS categories:

Category	Finding	Probability of malignancy	Recommendations
0	Incomplete, requires further evaluation	-	Additional imaging
1	Negative	0	Normal interval follow up
2	Benign	0	Normal interval follow up
3	Probably benign	<2	Short interval (6month) follow up
4	Suspicious for malignancy		Recommend biopsy
4a	Low	>2<10%	
4b	Moderate	>10<50%	
4c	High	>50<95%	
5	Highly suggestive of malignancy	>95	Appropriate action
6	Histologically proven malignancy	100	Treatment

Performance of sonographic BIRADS lexicon:

Lazarus et al analyzed the sonographic and mammographic results of 94 breast lesions using the BIRADS lexicon. They found a substantial agreement (kappa = 0.61, 0.66 & 0.69) for sonographic descriptors such as lesion shape, boundary and orientation, while a moderate agreement (kappa = 0.4 both) for margin and posterior acoustic features was found. Lesion echopattern was found to have fair (kappa = 0.20) interobserver agreement (21). For the final

BIRADS category, a fair agreement was observed (kappa = 0.28). It was concluded that interobserver agreement with the use of BIRADS lexicon was good and that the subdivision of category 4 into 4a, 4b and 4c was helpful in predicting the likelihood of malignancy (21).

A category 3 breast lesion at ultrasound implies a probably benign finding with a very low expectation of malignancy. It requires short interval follow up to establish stability of the findings. Management with imaging surveillance is based on the observation that the risk of malignancy is <2% in this category of lesions and that an interval change would be detected at imaging surveillance in the small percentage of lesions which are actually malignant(22).The recommended timing for follow up examination is however controversial as there is limited data available on the surveillance of category 3 lesions (23). A BIRADS 3 lesion at ultrasound carries a NPPV of more than 98%. However to avoid delay in diagnosis of the few malignant lesions in this category, a test which can improve the predictive value of this current system of assessment criteria would be highly desirable (24).

Category 4 carries a wide range of expected malignancy rates, anything from 2 to 94% (20). This category has been subdivided into 4a indicating low suspicion, 4b for intermediate and 4c for moderate suspicion. A malignancy rate of <10% is expected for 4a lesions therefore improved characterization of 4a lesions may be helpful in downgrading these lesions to category 3, thereby avoiding an invasive biopsy and managed with imaging follow up (24).

Limitations of the lexicon:

Interobserver variability in the interpretation of sonographic findings using the BIRADS lexicon has been evaluated by many studies. A poor interobserver agreement between category 4a and 4b was observed by Lazarus et al (21).

ELASTOGRAPHY – BASIC PRINCIPLES:

Elastography is an imaging technique which allows measurement of tissue stiffness. It measures the Young's E modulus, which is the parameter which corresponds to tissue stiffness (25).It was first described in the 1990s by Ophir et al, where a technique of measuring tissue elasticity in response to an external compressing force was introduced. Its clinical use in 1997 was initiated by Garra et al (26). Subsequently several studies have been performed with this technique, extending its application in a wide variety of clinical conditions such as thyroid, liver, breast, prostate, lymph node etc(18)

The three important components in physical examination of a patient include palpation, percussion and auscultation. Manual palpation assesses the position, hardness and mobility of a mass. Manual palpation is essentially determination of the elasticity of a tissue. Despite its indispensible utility in clinical examination, limitations of manual palpation include its subjective nature of assessment and its poor reliability in small and deeply located structures. Self-examination by manual palpation is advised as a home – screening tool for breast cancer. This is based on the fact that malignant lesions are harder as compared to the normal surrounding

tissue. It has been stated that even though the false positive rates are high with this practise, the benefits of early detection and timely treatment overweighs the costs involved (27)

Elastography has been referred to as ‘sonopalpation’ (25) because of its ability to provide similar information as clinical palpation with the advantage of being more objective than manual palpation.

Elasticity:

Elasticity is defined as the tendency of a material to regain its original size and shape following the application of an external force or stress. It is known that fluids possess volume elasticity, meaning that they resist change in volume while they do not resist change in shape. Solids on the other hand, resist change in volume and shape, implying that they possess volume elasticity and shear elasticity (27).

Strain:

Strain refers to the change in size or shape of the material. It is expressed as a ratio in terms of change in length per unit length (27).

It is equivalent to tissue stiffness, low strain corresponds to stiff tissue while high strain corresponds to a softer tissue (27). Strain is affected by changes in the structural composition of tissues for example in malignancy, strain decreases as the tissue becomes harder in consistency (28).

Stress:

Stress refers to the force acting on a unit area of the material, the SI unit for stress is Pascal = Newton /m2 (27).

Shear waves:

There are two principle modes of wave propagation in biological soft tissues depending on the direction in which the particles move during wave propagation. In longitudinal (also called compressional waves) waves, particles move along the direction of the propagation wave while in transverse waves which is also called shear waves, the particles move in a direction normal to the propagation wave (29).

Basic principles – the modulus of elasticity:

The modulus of elasticity refers to the ratio of stress / strain, which is a constant.

Three moduli are used to define elasticity:

1. Young's modulus (longitudinal elasticity), E = stress / strain
2. Shear / torsion modulus (rigidity), G
3. Bulk / volume modulus (volume elasticity), K

On applying stress on a material, its breadth contracts while it lengthens. This is defined by Poisson's ratio,

σ = lateral contraction per unit breadth / longitudinal extension per unit length

Three equations define the relationship between these 4 constants:

$G = E / (2(1+\sigma))$

$\sigma = (E/2G)-1$

$K = E / (3(1-2\sigma))$

Steps in elastography – determination of Young's modulus of a tissue (29):

Step 1 --- Excitation of the tissues of interest using an external force. This can be achieved with the use of mechanical means or acoustic radiation force.

Step 2 --- Detection of the changes in the tissue caused by the excitation. Static or dynamic displacement of the tissue occurs as a result of tissue excitation, shear waves being produced during dynamic displacement. This detection can be performed by using the Doppler effect, pulse echo methods or by acoustic emission.

Step 3 --- Display of the information in the form of images which can be in the form of spatial distribution of strains and shear waves or elastic moduli.

Techniques of elastography vary according to the means of excitation (25):

1. Static or Quasi-methods:

   In this method, a constant force is applied on the tissue and the resultant strain and displacement are measured using 2D correlation of USG images.

   Using this technique, a strain map also called the 'elastogram' is obtained. Since the applied stress is unknown, quantitative measurement of the Young's modulus is not possible with this method (25).

2. Dynamic methods:

   In this method, a short duration mechanical force or a fixed frequency oscillatory force is applied to the tissue. The resultant compressional / shear waves can be used to image the human body. For example, in conventional USG, high frequency compressional waves are used for imaging. Shear waves produced at low frequency (10-2000Hz) travel slowly, their speed being directly related to the shear modulus of the medium. Biological tissues are considered incompressible and the Young's modulus is taken as three times the shear modulus. A quantitative map of the tissue's Young modulus in other words the tissue stiffness can thus be obtained by using shear wave propagation speed (25).

Acoustic Radiation Force Impulse (ARFI):

In 2002, the concept of using short duration acoustic forces called push pulses to create local tissue displacements and detection of displacements by conventional ultrasound methods was introduced.

In strain elastography, the requirement of manual external compression is the greatest limitation because of its operator dependency which in turn affects the reproducibility of the test. In contrast, ARFI does not require the operator to apply external compression; hence it is more objective and reproducible. In ARFI imaging, under the influence of a pushing pulse on a focal point, Shear waves travel away from this point and by measuring the speed of these waves, the value of shear modulus can be derived (25,27).

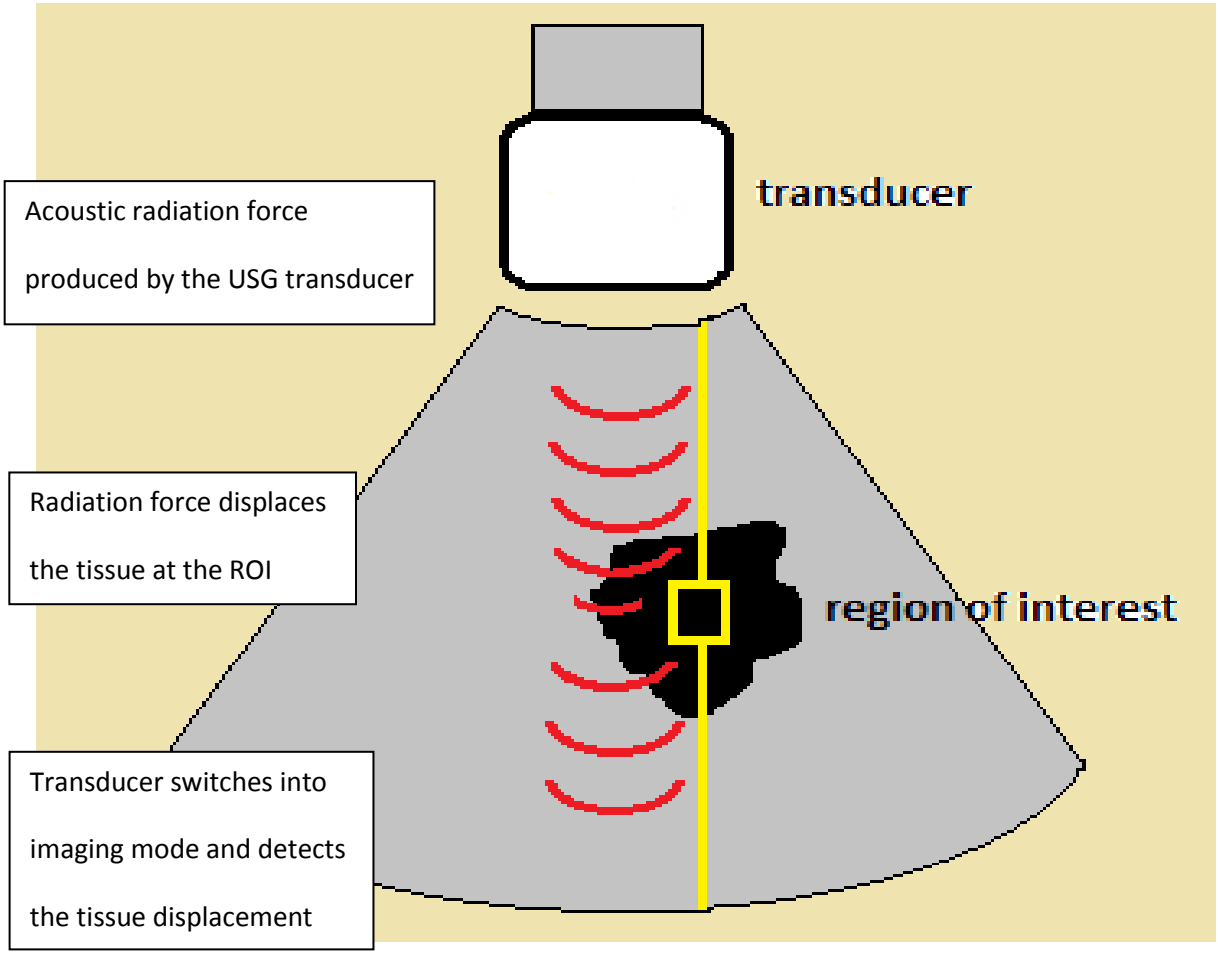


Figure 2: schematic diagram showing the principle of ARFI imaging.

There are two components of imaging in ARFI:

1) Virtual touch quantification (VTQ):

   VTQ provides a quantitative measure of tissue stiffness.

   Technique: The area of interest is imaged with B mode ultrasound and a region of interest box (ROI) is placed within the lesion, following this, the transducer applies a 'pushing pulse' which produces localized tissue displacement. This in turn produces 'shear waves' which are detected by the same transducer using conventional USG tracking beams.

   The time to peak displacement at various locations is measured and using this information, the shear wave velocity can be derived. The shear wave speed is related to the square root of tissue elasticity. It is expressed in terms of meters / second.

2) Virtual touch imaging (VTI):

   This method provides a qualitative grayscale map of tissue stiffness.

   Technique: In this method, the entire lesion is placed within the ROI box, and the VTI mode is activated. The resultant image is a grey scale display of tissues stiffness on one side and B mode image on the other side on a dual screen.

Image interpretation:

Elastography can be interpreted in two ways (17):

1. Qualitative – by assessing the strain pattern. Colour coded images superimposed on B-mode ultrasound images are available in commercially available units. The final information can be interpreted with elasticity scores in a subjective manner.

2. Semi quantitative – by calculating the strain and length/area ratio.

There are several classification systems for scoring strain elastographic patterns:

a) Elasticity scoring by Itoh et al (30):

Score	Strain image	Colour coded map
1	Strain appears in entire hypoechoic area	Entire lesion is shown in green, same as the surrounding normal breast
2	Strain does not appear in some parts of the hypoechoic area	Mosaic of green & blue
3	Strain appears in the periphery of the lesion and not at the centre of the hypoechoic area	Centre of the lesion is blue, peripheral areas appear green
4	No strain appears within the hypoechoic area	Entire lesion is blue

5	No strain appears within the hypoechoic area, including the surrounding areas	Lesion along with surrounding area is blue

A score of 1 to 3 indicated a benign lesion while a score of 4 and 5 indicated a malignant lesion.

b) Tsukuba University score: adapted according to Itoh and Ueno.

c) Leong strain patterns (31):

1 - homogeneously black

2 - heterogeneously black with small scattered white areas

3 - homogeneously white,

4 - heterogeneously white with small scattered black areas

5 - bull's eye sign

Advantages of ARFI:

1. Less operator dependent because manual compression is not required.
2. Consistent compressing force produced by the transducer.

Review of relevant studies on elastography:

Many studies have evaluated the use of elastography in breast lesions, using both strain and shear wave elastography techniques.

Itoh et al in 2006, were the first group to use elastography as diagnostic modality in the assessment of breast lesions and they proposed a 5 point scoring system based on the visual assessment of strain patterns. Appearance of strain in the entire hypoechoic area of the lesion was scored as 1, strain not seen in part of the hypoechoic area was scored as 2, strain seen in only in the peripheral areas and not at the centre of the hypoechoic area was scored as 3, no strain seen in the entire hypoechoic area was scored as 4 and no strain either in the hypoechoic area or surrounding area was scored as 5. A score of 1 to 3 was considered benign while a score of 4 and 5 indicated malignancy. In their study, they found a higher sensitivity with the use of elastography compared to conventional B-mode ultrasound (30).

Zhi et al in 2007, studied the comparative diagnostic accuracy of mammography, B mode sonography and ultrasound elastography on 296 breast lesions and found similar sensitivity and negative predictive values among these three modalities, with the specificity and positive predictive value of ultrasound elastography being significantly higher than the other two modalities ($p<0.5$). They also found that a combination of elastography and conventional sonography yielded the highest accuracy ($p<0.5$) for detection of malignancy (18).

Sohn et al in 2009 found no statistically significant difference in the diagnostic performance of combining elastography and conventional ultrasound as compared to conventional ultrasound alone. However in the evaluation of elastography as a diagnostic tool, a better diagnostic accuracy was observed with the use of area ratio on strain elastography as compared to the use of visual elasticity scoring method when used as a criterion for determining malignancy (32).

Leong et al in 2010 studied the diagnostic performance of conventional USG and combined USG with elastography on 110 breast lesions. There was no difference in the sensitivity of the modalities however specificity and accuracy of elastography and combined imaging was found to be significantly higher than conventional USG alone ($p < 0.001$). It was also observed that the use of strain patterns was not as specific as the use of distance and area ratios (31).

Navarro et al in 2011 found elastography to have a lower sensitivity compared to conventional ultrasound (69.5% vs. 96.6% respectively) however, with a higher specificity compared to ultrasound (83.1% vs. 76.9% respectively)(33).

Jung et al in 2012, using breast tissue specific imaging preset in elastography, found that the strain ratio had the best performance in terms of diagnostic accuracy, the sensitivity, specificity, PPV and NPV being 86%, 85.1%, 78.7% and 90.5% respectively (34).

Berg et al in 2012 stated that the addition of elastographic findings to the BIRADS feature increased the specificity of the test without affecting the sensitivity. They concluded that this modality could potentially reduce the number of unnecessary biopsies in the category of BIRADS 4a lesions (24).

Sadigh et al in 2012 performed a meta-analysis on the accuracy of elastography in differentiating between malignant and benign breast masses, specifically looking into the quantitative parameters (strain ratio and length ratio) which included 9 different studies, comprising a total of 2087 breast masses. The summary sensitivity was found to be 88% with a specificity of 83%, positive and negative likelihood ratios being 5.57 and 0.14 respectively. It was concluded that combination of elastographic techniques with conventional B mode ultrasonography may be potentially beneficial (28). In another meta-analysis by the same group, which included 29 studies comprising of 5511 masses, 2065 malignant and 3446 benign, they found that the use of elastography alone was not superior to conventional ultrasound. They recommended that low risk patients may benefit from elastography following a positive ultrasound to decrease rate of unnecessary biopsy (35).

Evans et al in 2012 also observed a superior sensitivity when elastography was combined with B-mode USG (sensitivity 100%, specificity 61%, PPV 82% and NPV100% for combined modality and sensitivity 95%, specificity 69%, PPV 84%, NPV 91% for B-mode alone) (36).

Bai et al in 2012 concluded that the use of shear wave quantification can reliably differentiate benign from malignant lesions and that the use of 'X.XX' reading as a cut off for malignancy can increase the specificity and positive predictive value to 100% (37).

Jin et al in 2012 observed that the use of SWV ratio (between the lesion and surrounding tissue) produced a higher accuracy in the prediction of malignancy (38).

Zhou et al in 2013 found a significant difference in the SWVs measured within the lesion, boundary of lesion and surrounding parenchyma between the benign and malignant groups. They also observed that the highest SWV was seen in grade 3 invasive ductal cancer (39).

Chang et al in 2013 found similar performance between strain and shear wave elastography, with improved overall performance when either of them was combined with B mode ultrasound (40).

Alhabshi et al also found similar results of improved performance with combination of elastography and B-mode USG (sensitivity 100%, specificity 93%, PPV 99% and NPV 90%) compared to B-mode USG alone (sensitivity 97%, specificity 61.4%, PPV 62.5% and NPV 96.8%) (41).

The recent published study on elastography by Kim et al in 2014 studied the diagnostic performance of combined B-mode ultrasonography (BUS), acoustic radiation force impulse (ARFI) elastography, and strain ratio (SR) comparing it with the use of B-mode USG alone. They found a higher performance when the 3 modalities were combined as compared to BUS alone ($p< 0.01$) (42).

Summary of recent studies on elastography:

Elastography using VTI elasticity scores (ES):

Author	Total	Bng	Mlg	Mean ES (Bng)	Mean ES (Mlg)	Cut off score	Sen (%)	Sp (%)
Kim et al, 2014	157	40	117	1.6±0.8	3.7±1	Between 2 & 3	77.5	93.2

Elastography using VTI Area Ratio:

Author	Total	Bng	Mlg	Mean AR (Bng)	Mean AR (Mlg)	Cut off AR	Sen (%)	Sp (%)
Meng et al, 2011	92	65	27	1.08±0.21	1.99 ±0.63	-	-	-
Jin et al, 2012	122	66	56	1.09±0.17	1.96±0.64	1.37	76.8	93.9

Elastography using VTQ shear wave velocity:

Author	Total	Bng	Mlg	SWV (Bng)	SWV (Mlg)	Cut off (SWV)	Sen (%)	Sp (%)	Acc (%)
Kim et al, 2014 (42)	157	40	117	2.22±0.88	4.23±1.09	3.52	97.5	91.5	93
Tozaki et al, 2013 (43)	83	-	-	-	-	VTQ VTI	86 88	90 93	88 90
Zhou et al, 2013 (39)	175	108	67	2.68±1.2	5.62±3.26	4.19	55.2	95.8	70
Meng et al, 2011 (44)	92	65	27	3.25±2.03	8.22 ±1.27	-	-	-	-
Jin et al, 2012 (38)	122	66	56	2.44±1.27	5.74±1.68	3.65	89.3	80.3	-
Bai et al, 2012 (37)	143			2.25±0.59	5.96±2.96	3.06	75.6	95.1	85.6
Tozaki et al, 2012 (45)	161	18	43	-	-	3.59	91	93	92
Tozaki et al, 2011 (46)	30	13	17	2.68	4.49	-	-	-	-

MATERIALS AND METHODOLOGY

Study design: Study of diagnostic test accuracy

Study type: Analytical

Setting:

Christian Medical College (CMC) Vellore is a 2700 bedded tertiary care centre in northern Tamil Nadu.

Inclusion criteria:

1) Consecutive patients with solid breast masses – solid / mixed with solid component >1cm.

2) Size >1cm.

3) Histopathological diagnosis after ARFI.

Exclusion criteria:

1) Calcified lesions with non-calcified area <1cm

2) Prior biopsy/FNAC/surgery/radiation on the same breast

Sampling and consent:

Patients who were referred from the outpatient department (predominantly from the surgical and gynaecological outpatient department) for an ultrasound of the breast with clinical data of a palpable breast lump and those patients with non-palpable lumps detected on screening mammography were enrolled during the course of this prospective study.

All the patients were filtered through the exclusion and inclusion criteria and only those patients who fulfilled the specifications were enrolled in the study. No specific sampling strategy was employed to enrol patients; all consecutive patients fulfilling the criteria were included. The selection of the study population was independent of the results of the reference standard (histopathology).

Prior to the examination, informed written consent was obtained from the patient / patient's relative (consent form and patient information sheet attached in Annexure2).

Data of all the patients were entered into a coded proforma (Annexure 1).

Timing:

The time period between the index study and the reference standard would range between 2-3 days. The lesion is unlikely to change in this short time period.

Equipment:

The ARFI study was performed with Siemens ACUSON S2000 using high frequency linear array probe 9L4, frequency of ~4-9MHz. The B-mode imaging assessment was done prior to the ARFI assessment using the same machine with high frequency linear array probe 9L4, frequency of ~4-9MHz.

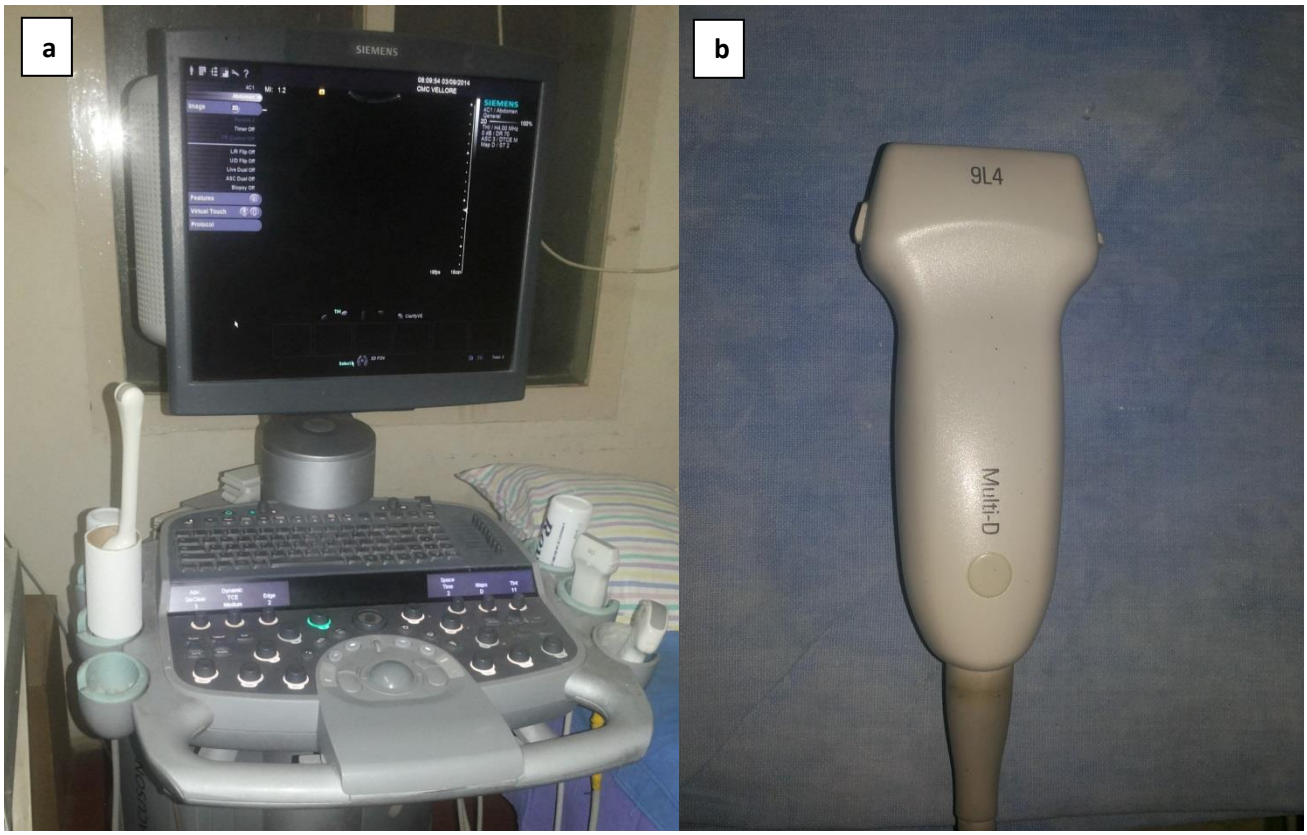


Figure3: Siemens ACUSON S2000 ARFI machine (a) and high frequency linear array probe 9L4, frequency of ~4-9MHz (b).

Technique of examination:

1) B-mode USG:

With the patient in supine position and arm raised over the head, B-mode assessment of the breast lesion was made using the BIRADS lexicon (4th edition) and the final BIRADS category determined.

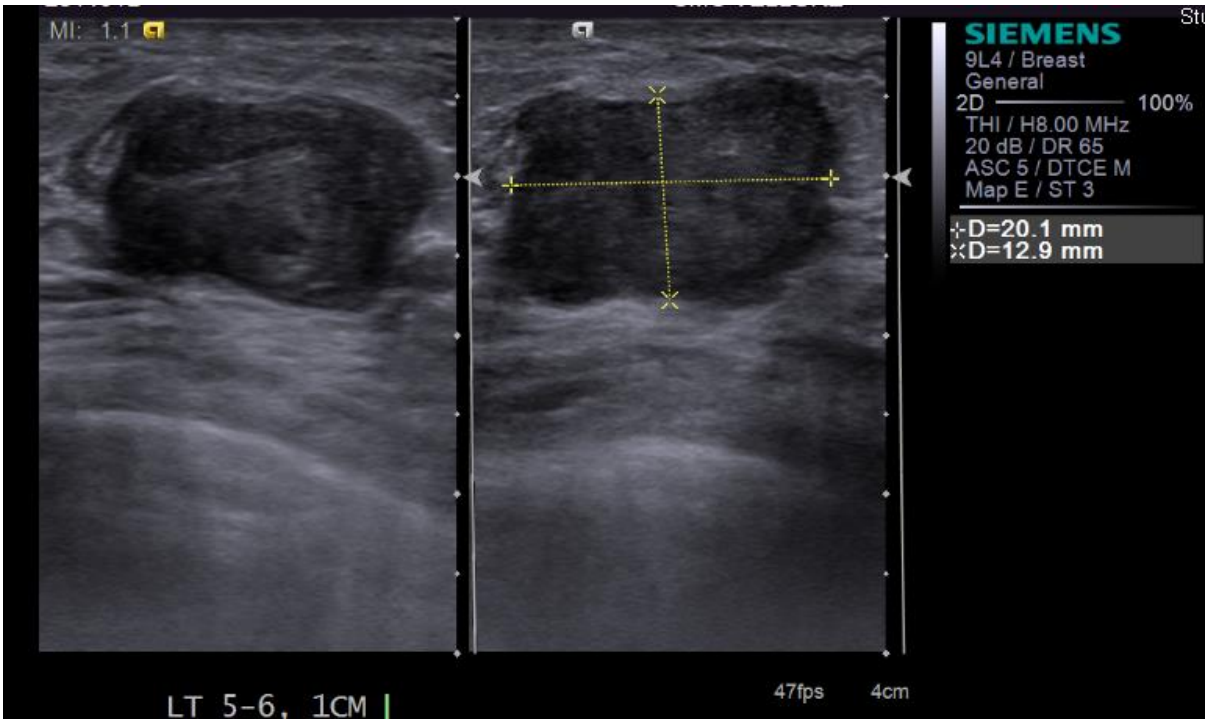


Figure 4: B-mode USG acquisition of the breast lesion.

2) Virtual Touch Imaging (VTI):

VTI was performed using good amount of gel and light pressure to ensure good skin contact. With the VTI mode turned on, a dual screen appears and the lesion is entirely placed within the region of interest (ROI) box, with the patient in suspended respiration, VTI is activated. This results in a B-mode image on the left hand side of the screen and a grey scale VTI image on the right hand side. The area of the lesion on B-mode and VTI were then measured and the ratio calculated.

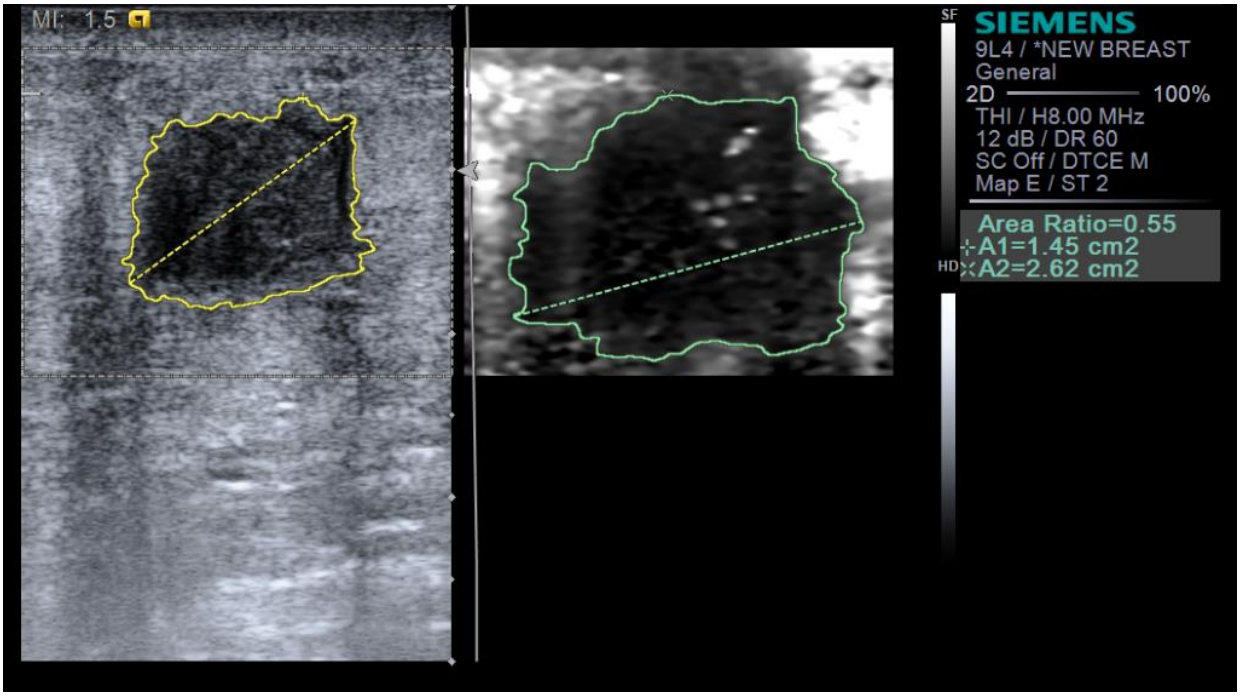


Figure 5: VTI mode - B-mode image on the left hand side of the screen with the corresponding VTI image on the right hand side. Strain depicted as dark areas on the VTI image. Area of the lesion measured on B-mode followed by area measurement on VTI image. The Area ratio is measured by dividing the area measurements.

3) Virtual Touch Quantification (VTQ):

Using the same technique of light pressure and suspended respiration, VTQ was performed by placing the region of interest (ROI) box (size 0.5x0.5cm) entirely within the lesion at a maximum depth of 4cm. Once the VTQ mode is activated, the Shear Wave Velocity within the lesion is displayed on the right hand side of the screen.

Five measurements were obtained from within the lesion and in the perilesional tissue at the same depth (not less than 1cm from the lesion) and the average of both were calculated.

Lesions showing repeated 'X.XX m/s' readings were recorded as 9m/s (maximum measurable reading by the machine).

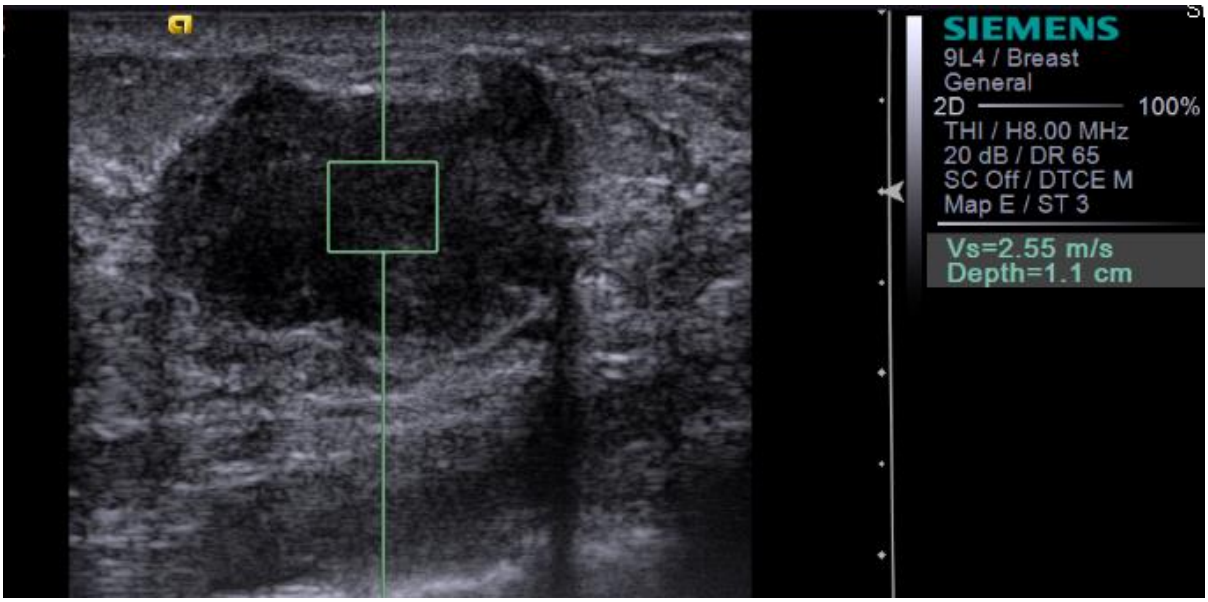


Figure 6: VTQ – measurement of shear wave velocity within the lesion.

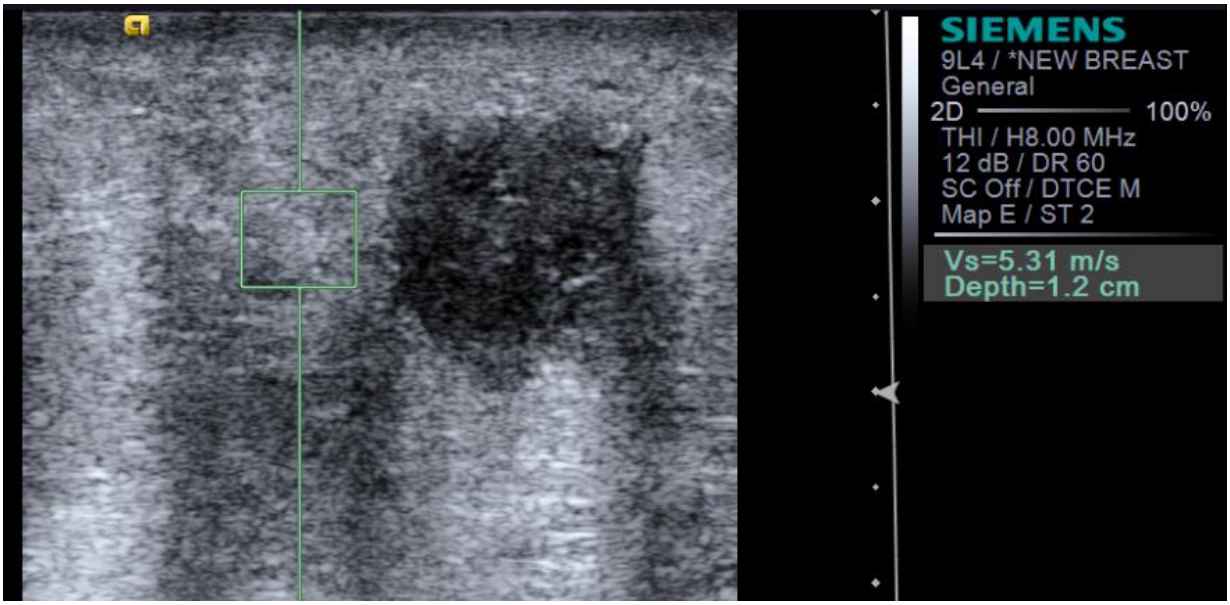


Figure 7: VTQ – measurement of shear wave velocity in the surrounding tissue.

Image Interpretation:

The images were viewed and interpreted by the principal investigator with the help of one co-investigator with experience in breast imaging. The observers were blinded to the patient's histopathology reports. All the data were recorded in the proforma (Annexure 2)

1) B-mode image interpretation:

BIRADS lexicon (4th edition):

Shape: Oval / Round / Irregular

Margin: Circumscribed / Microlobulated / Indistinct / Angular/ Spiculated

Orientation: Parallel / Anti-parallel

Boundary: Abrupt interface / Echogenic halo

Echopattern: Hyperechoic / Isoechoic / Hypoechoic / Complex

Posterior acoustic features: Enhancement / Shadowing

Calcification: Macrocalcification / Absent / Microcalcification

BIRADS category:

All lesions were classified into one of the following categories based on the sonographic descriptors:

BIRADS 3 – probably benign

BIRADS 4a – low suspicion of malignancy

BIRADS 4b – moderate suspicion of malignancy

BIRADS 4c – high suspicion of malignancy

BIRADS 5 – highly suggestive of malignancy

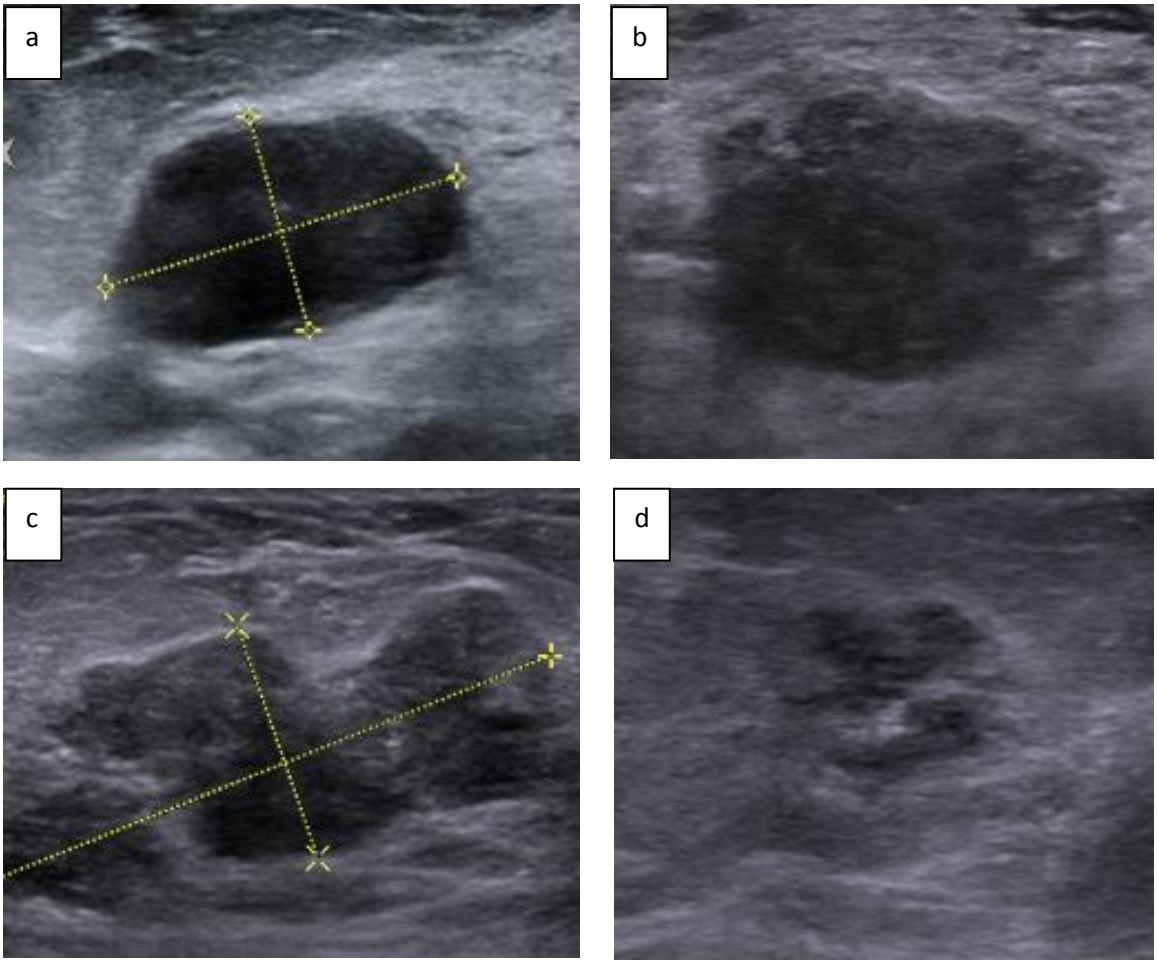


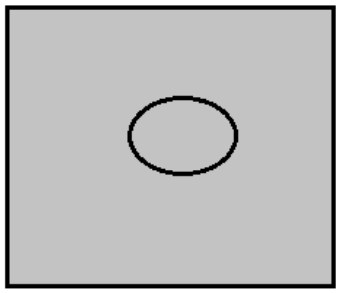
Figure8: a) BIRADS 3 – well-defined, oval, hypoechoic lesion with posterior acoustic enhancement b) BIRADS 4a – well-defined hypoechoic lesion with microlobulations c) BIRADS 4b -irregular shaped with complex echopattern d) BIRADS 4c - ill-defined lesion with complex echopattern and microcalcification e) BIRADS 5 - ill-defined spiculated hypoechoic mass with echogenic halo.

2) VTI image interpretation:

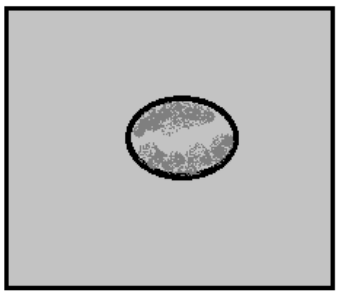
Visual assessment was performed and the lesions were given a score from 1 to 5 based on the 5 point scoring proposed by Itoh and Ueno.

Elasticity scores:

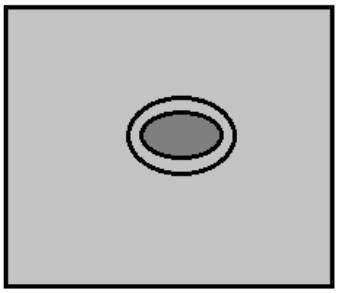
Score 1 = same as surrounding tissue.



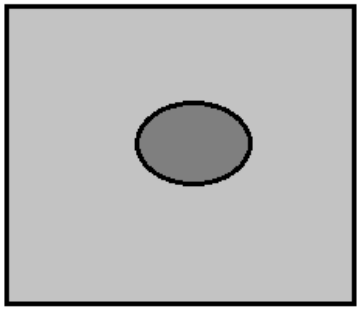
Score 2 = mosaic, same size.



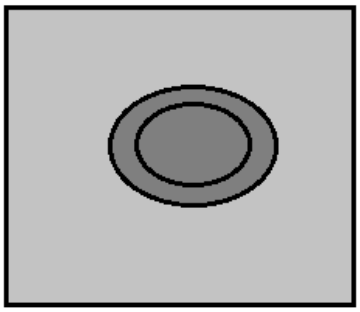
Score 3 = centre darker, same size.



Score 4 = darker than surrounding tissue, same size.



Score 5 = darker than surrounding tissue, larger size.



Elasticity score of 1 to 3 were considered benign while a score of 4 and 5 were considered malignant.

Area ratios:

Area of the lesion was traced on the B-mode image and VTI image. Using these values, area ratios were calculated for each lesion. Assessment of area ratio was not performed in lesions where the ROI box could not include sufficient normal surrounding tissue.

3) VTQ image interpretation:

The shear wave velocity measurement appears on the right hand side of the screen. The measurement values obtained within the lesion and surrounding tissues were separately recorded in the proforma.

Shear wave velocity ratios between the lesion and surrounding normal tissue were calculated.

Repeated readings of 'X.XX' were recorded as 9.00m/s which is the limit measurable by the machine.

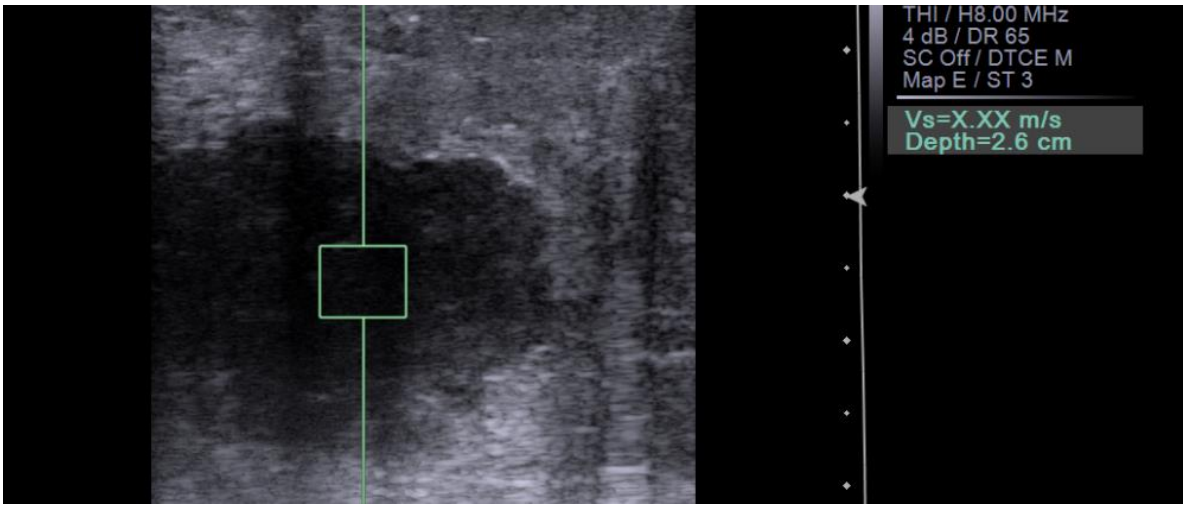


Figure 9: VTQ – shear wave velocity shown as 'X.XX' m/s within the lesion.

Histopathological Examination:

Histopathology was the standard of reference (gold standard). The lesions were broadly divided into benign and malignant groups for analysis. Hormone receptor and HER2NEU status was performed for all invasive carcinomas.

Institutional Review Board approval:

This study was approved by the Institutional review board (IRB) prior to the commencement of the study (IRB minutes number. 8564 dated 12.11.2013) (Annexure 3).

Statistical analysis:

Statistical analysis was performed using SPSS software version 16.

1) The descriptive data were expressed in mean ± standard deviation.

2) Student's t-test (Independent samples) was used for comparing mean SWV values, SWV ratios and area ratios.

3) Receiver operating characteristic (ROC) curves were drawn to compare the diagnostic performance of B-mode ultrasound, VTI, VTQ and combined VTI + VTQ.

4) Best cut-off values for lesion SWV, SWV ratio, area ratio and elasticity scores for predicting malignancy were obtained from ROC curve analysis.

5) Calculation of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy were performed using the best cut-off values.

6) Correlation coefficient was calculated using bivariate analysis.

7) P values based on 2-sided testing and P value< 0.05 was taken as statistically significant.

ANALYSIS AND RESULTS

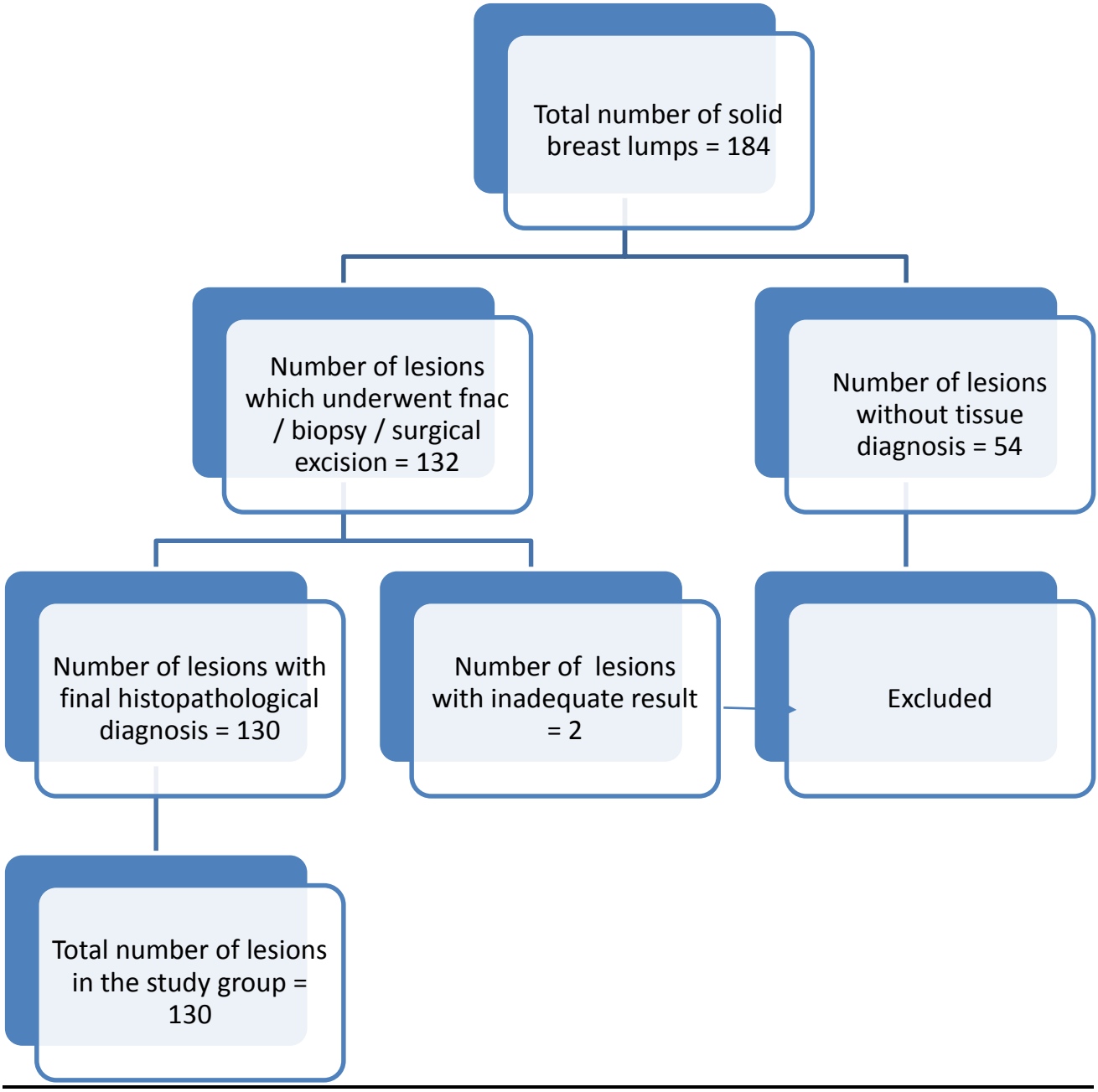


Figure 10: Flow diagram of the study.

STUDY DESIGN

Duration of study:

The study patients were prospectively recruited over a period of 10 months, from November 2013 to August 2014.

Sample size:

A total of 124 patients with 184 lesions were assessed with B-mode USG and ARFI elastography. Among these, 132lesions underwent tissue diagnosis in the form of fine needle aspiration cytology, image guided biopsy or surgical excision biopsy for confirmation of diagnosis. 2 among these 132 lesions had an inadequate yield and histopathological confirmation could not be obtained. 54 lesions did not have histopathological confirmation and were excluded from the analysis.

Hence, the total number of lesions in the final analysis was 130.

PATIENT DEMOGRAPHICS:

(1) Age Distribution

The mean age of the participant population was 35 years (range 14-66 years)

(2) Sex Distribution

Out of the 124 patients, 122 were female (98.4%) and 2 were male (1.6%).

LESION CHARACTERISTICS:

Size:

The mean lesion diameter was 23.6mm (range 10-64mm)

Clinical palpation:

Out of the 184 masses, 147 lesions (80%) were clinically felt as hard lesions, 35 lesions (19%) were considered soft to palpation, while 2 lesions (1%) were non-palpable clinically.

Histopathological types:

There were 95 (73.1%) benign lesions and 35 (26.9%) malignant lesions (figure 10).

1) Benign subtypes:

   Fibroadenoma (n= 81)

   Adenosis (n= 6)

   Inflammatory (n= 4)

   Benign phyllodes (n= 3).

2) Malignant subtypes:

Invasive ductal carcinoma (n=33)

Invasive lobular carcinoma (n=1)

Medullary carcinoma (n=1)

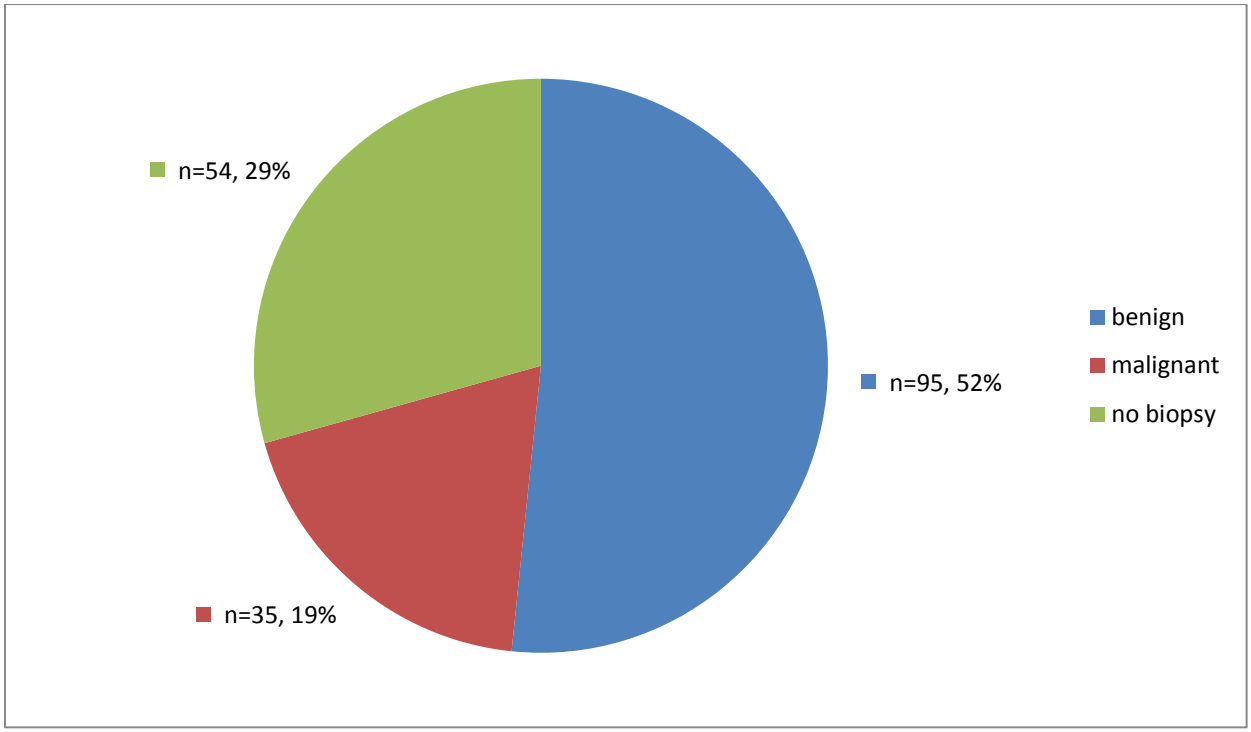


Figure 11: Pie chart showing the number of benign and malignant lesions along with the number of lesions without histopathological confirmation (these were excluded from the study)

B-mode features:

1) Shape: Of the 184 masses, 122 lesions (66.3%) were oval, 8 lesions (4.3%) were round and 54 lesions (29.3%) were irregular in shape.

2) Margin: 110 lesions (59.8%) were well-circumscribed, 39 lesions (21.2%) had microlobulations, 13 lesions (7.1%) had indistinct margins, 8 lesions (4.3%) had angular margins and 14 lesions (7.6%) had spiculated margins.

3) Orientation: 155 lesions (84.2%) had parallel orientation and 29 lesions (15.8%) were anti-parallel.

4) Boundary: 143 lesions (77.7%) had an abrupt interface while 41 lesions (22.3%) had an Echogenic halo.

5) Echopattern: 165 lesions (89.7%) were hypoechoic, 12 lesions (6.5%) were complex, 4 lesions (2.2%) were hyperechoic and 3 lesions (1.6%) were isoechoic.

6) Posterior acoustic features: 164 lesions (89%) showed enhancement while 20 lesions (11%) showed posterior acoustic shadowing.

7) Calcification: 159 lesions (86.4%) did not show calcification, 16 lesions (8.7%) showed macrocalcification and 9 lesions (4.9%) showed microcalcification.

8) BIRADS category: 98 lesions (53.3%) were classified as BIRADS 3, 18 lesions (9.8%) as BIRADS 4a, 23 lesions (12.5%) as BIRADS 4b, 20 lesions (10.9%) as BIRADS 4c and 25 lesions (13.6%) as BIRADS 5 (figure 11).

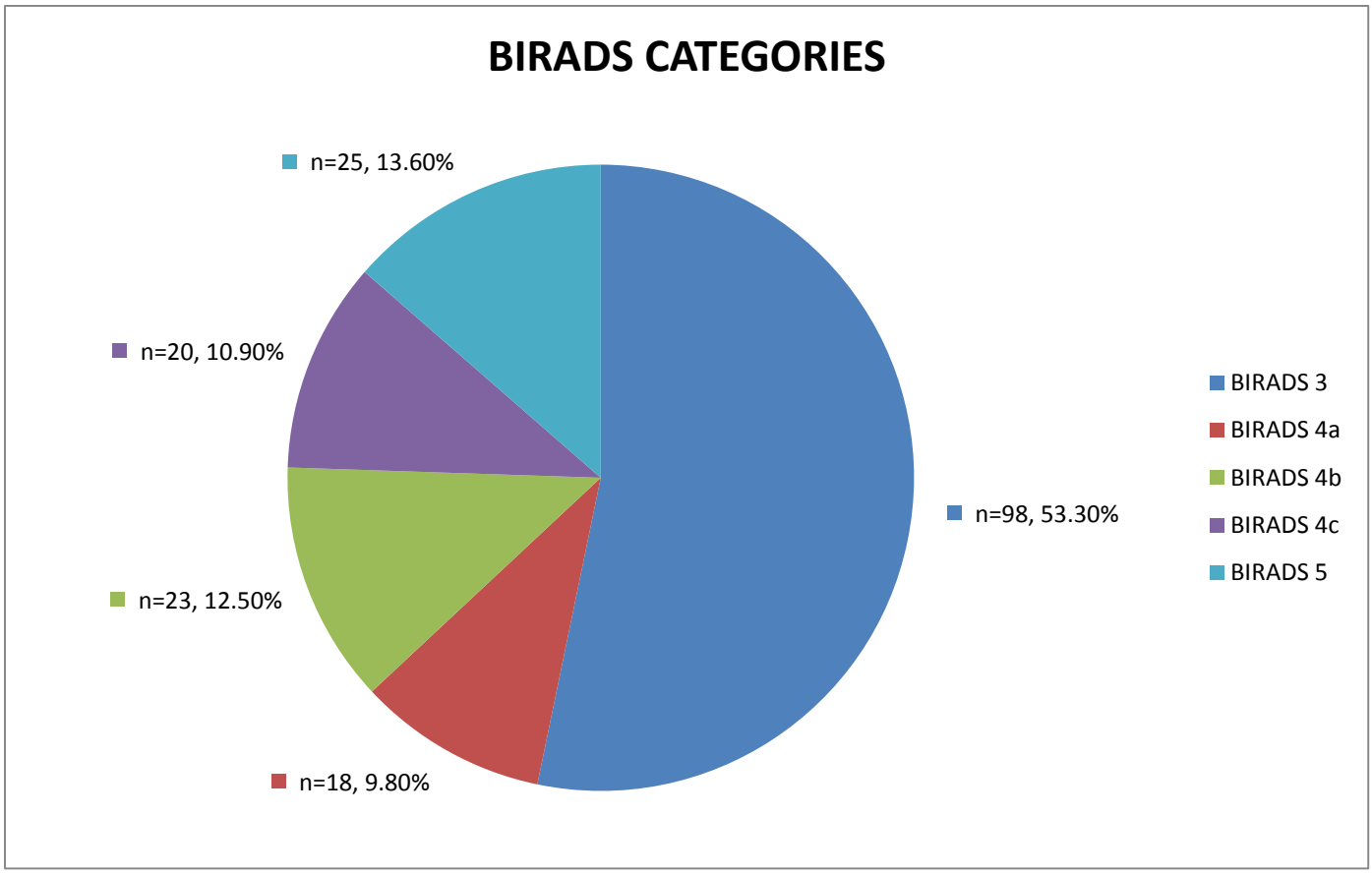


Figure 12: Pie chart showing the number of lesions in each BIRADS category.

Features	Benign	Malignant
Clinical palpation		
Hard	4.3% (n=4)	82.9% (n=29)
Soft	95.7% (n=89)	17.1% (n=6)
Shape		
Oval	76.8% (n=73)	14.3% (n=5)
Round	3.2% (n=3)	2.9% (n=1)
Irregular	20% (n=19)	82.9% (n=29)
Margin		
Well-circumscribed	69.5% (n=66)	2.9% (n=1)
Microlobulated	24.2% (n=23)	28.6% (n=10)
Indistinct	3.2% (n=3)	25.7% (n=9)
Angular	1.1% (n=1)	8.6% (n=3)
Spiculated	2.1% (n=2)	34.3% (n=12)
Orientation		
Parallel	91.6% (n=87)	45.7% (n=16)
Anti-parallel	8.4% (n=8)	54.3% (n=19)
Boundary		
Abrupt interface	90.5% (n=86)	14.3% (n=5)
Echogenic halo	9.5% (n=9)	85.7% (n=30)
Echopattern		
Hyperechoic	3.2% (n=3)	---

Isoechoic	1.1% (n=1)	---
Hypoechoic	90.5% (n=86)	85.7% (n=30)
Complex	5.3% (n=5)	14.3% (n=5)
Posterior acoustic features		
Enhancement	93.7% (n=89)	65.7% (n=23)
Shadowing	3.7% (n=6)	34.3% (n=12)
Calcification		
Macrocalcification	10.5% (n=10)	2.9% (n=1)
Absent	87.4% (n=83)	82.9% (n=29)
Microcalcification	2.1% (n=2)	14.3% (n=5)

Table 1: The BIRADS descriptors with final histopathological diagnosis.

BIRADS category on B-mode	Benign	Malignant
3	60% (n=57)	2.9% (n=1)
4a	13.7% (n=13)	--
4b	17.9% (n=17)	5.7% (n=2)
4c	6.3% (n=6)	28.6% (n=10)
5	2.9% (n=2)	62.9% (n=22)

Table 2: BIRADS category with final histopathological diagnosis

VTI findings:

1) Elasticity scores:

Of the 184 lesions, 20 lesions (11.3%) had an elasticity score of 1, 77 lesions (43.5%) had score 2, 32 lesions (18.1%) had score 3, 5 lesions (2.8%) had score 4 and 43 lesions (24.3%) had score 5 (figure 12)

Elasticity pattern could not be assessed in 7 lesions as the ROI box could not include sufficient surrounding tissue.

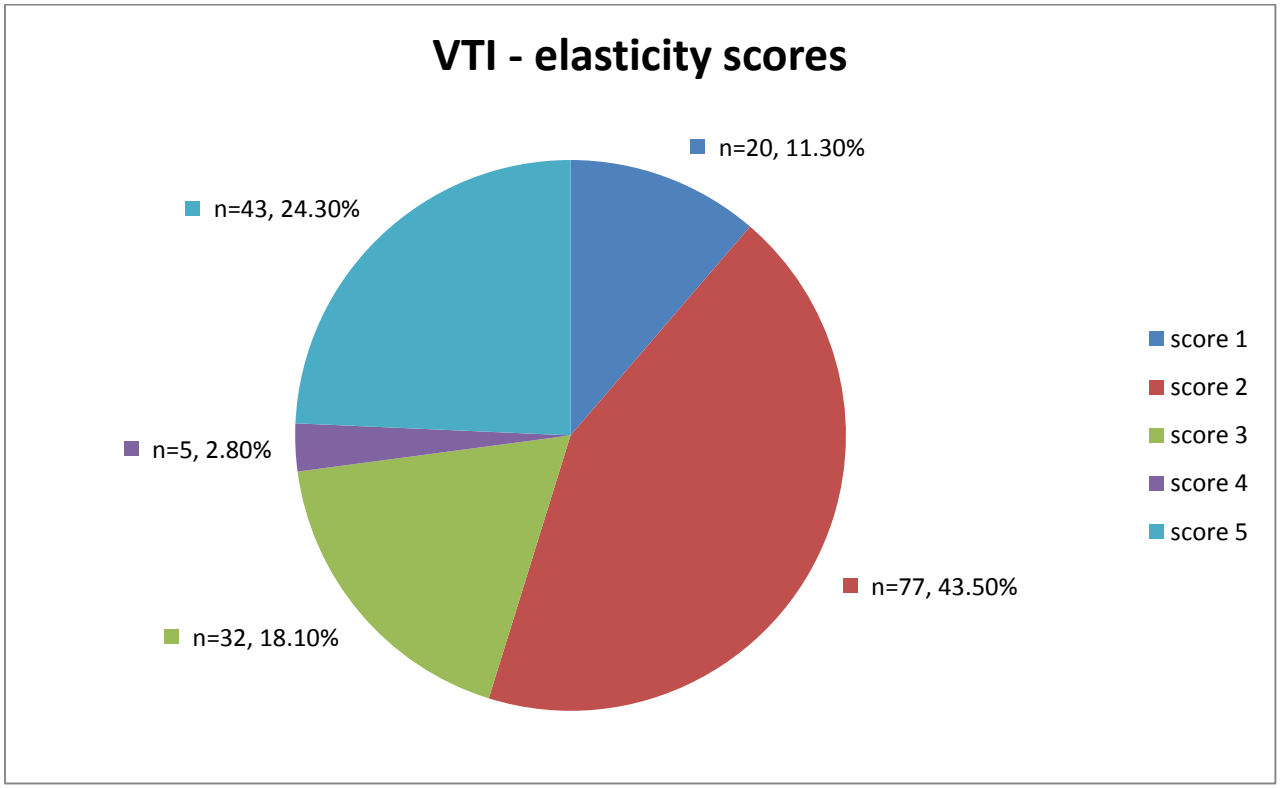


Figure 13: Pie chart showing the distribution of elasticity scores among the breast masses.

Using the 5 point visual scoring system, 88 of the benign lesions were correctly given a 'benign' elasticity score (score 1, 2 and 3) while 7 benign lesions were misclassified as 'malignant' on VTI visual assessment. All the 35 malignant lesions had an elasticity score of 4 or 5 on VTI and were correctly classified as 'malignant'. Findings are given in table 3.

There was significant difference in the elasticity scores between the two groups (chi square = 104.45, df = 4, $p<0.001$)

Histopathology	VTI				
	1	2	3	4	5
Benign	13.7% (n=13)	50.5% (n=48)	28.4% (n=27)	2.1% (n=2)	5.3% (n=5)
Malignant	---	---	27	2.9% (n=1)	97.1% (n=34)

Table 3: benign and malignant lesions with their elasticity scores on VTI

Combined VTI score	Benign	Malignant
1 -3	92.6% (n=88)	7.4% (n=7)
4-5	---	100% (n=35)

Table 4: histopathology and combined VTI scoring (score 1-3 as benign and 4-5 as malignant)

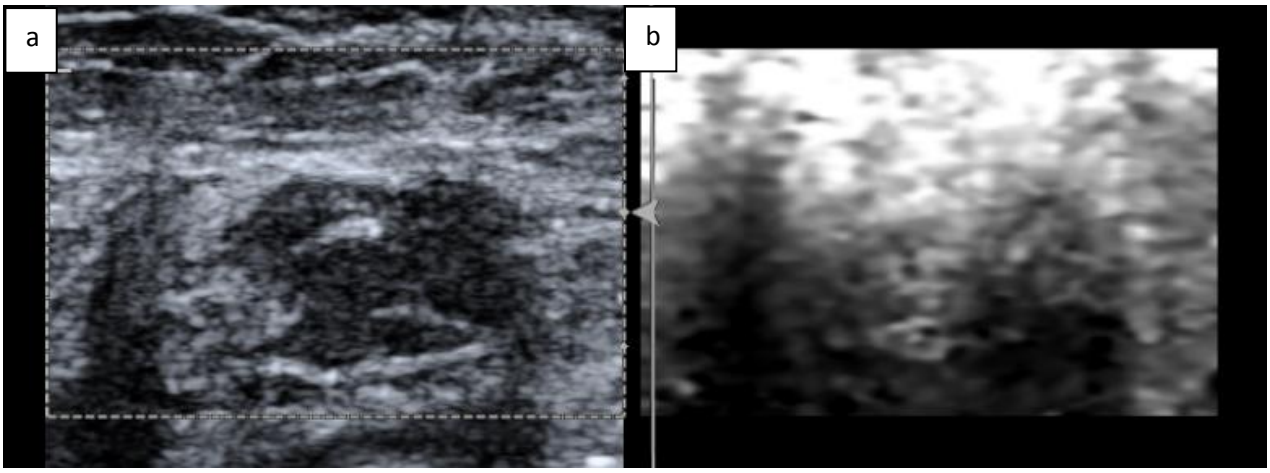


Figure 14: **elasticity score 1** – a) B-mode USG image showing a well-defined hypoechoic lesion.

b) VTI image showing strain pattern similar to the surrounding breast parenchyma.

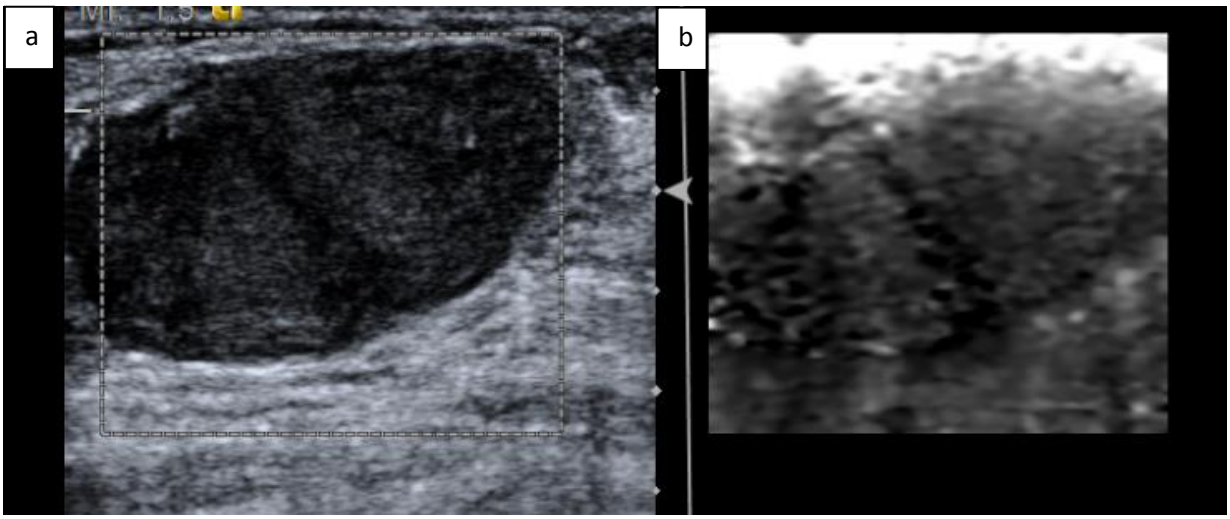


Figure 15: **elasticity score 2** – a) B-mode USG image showing a well-defined hypoechoic lesion.

b) VTI image showing a mosaic pattern with a mixture of dark and bright areas within the lesion.

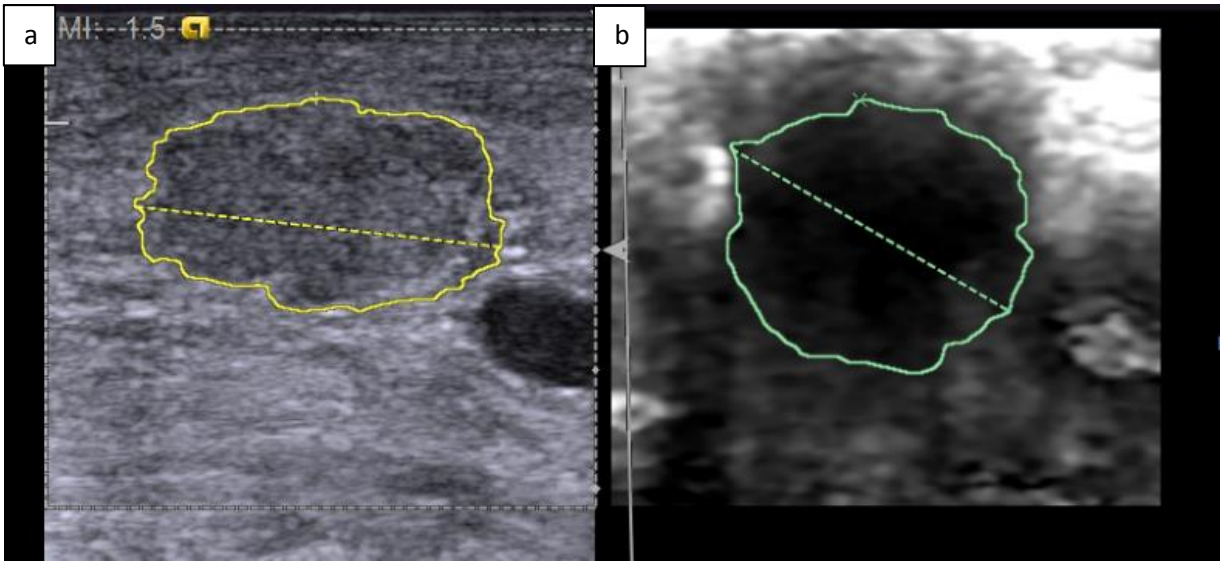


Figure 16: **elasticity score 3**– a) B-mode USG image showing a well-defined iso-to hypoechoic lesion. b) VTI image showing a darker area within the centre of the lesion, no increase in size.

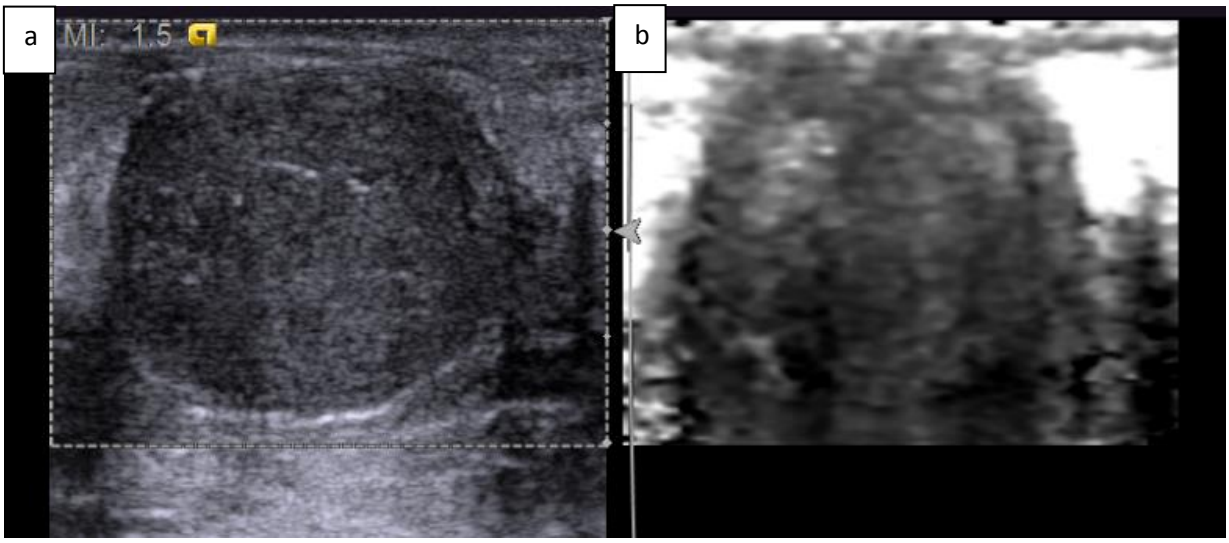


Figure 17: **elasticity score 4**– a) B-mode USG image showing a well-defined hypoechoic lesion. b) VTI image showing a darker pattern throughout the lesion with no increase in size.

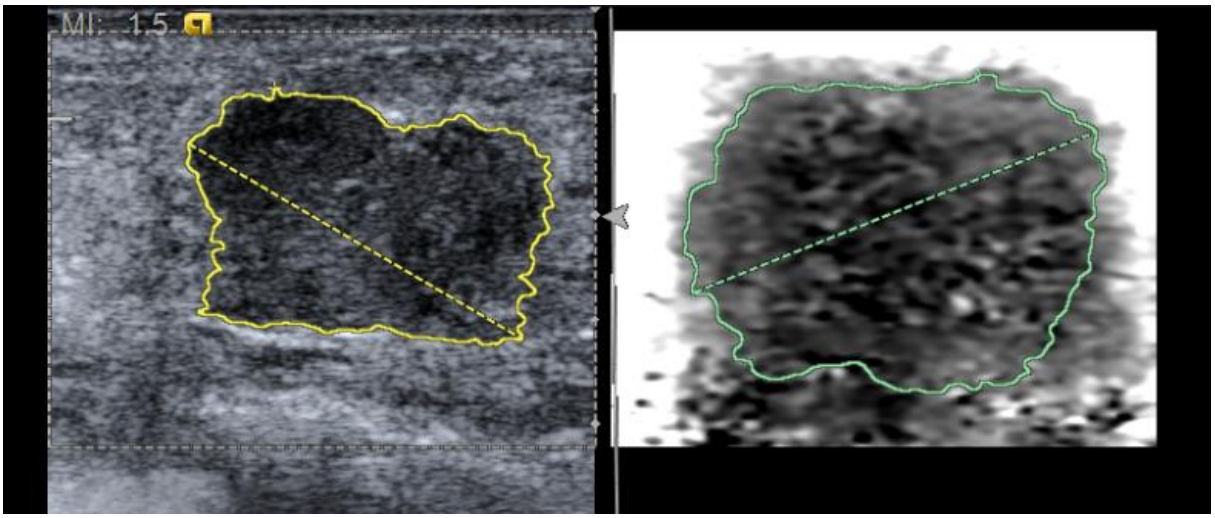


Figure 18: **elasticity score 5**– a) B-mode USG image showing a well-defined hypoechoic lesion. b) VTI image showing a darker pattern within the lesion with increase in size.

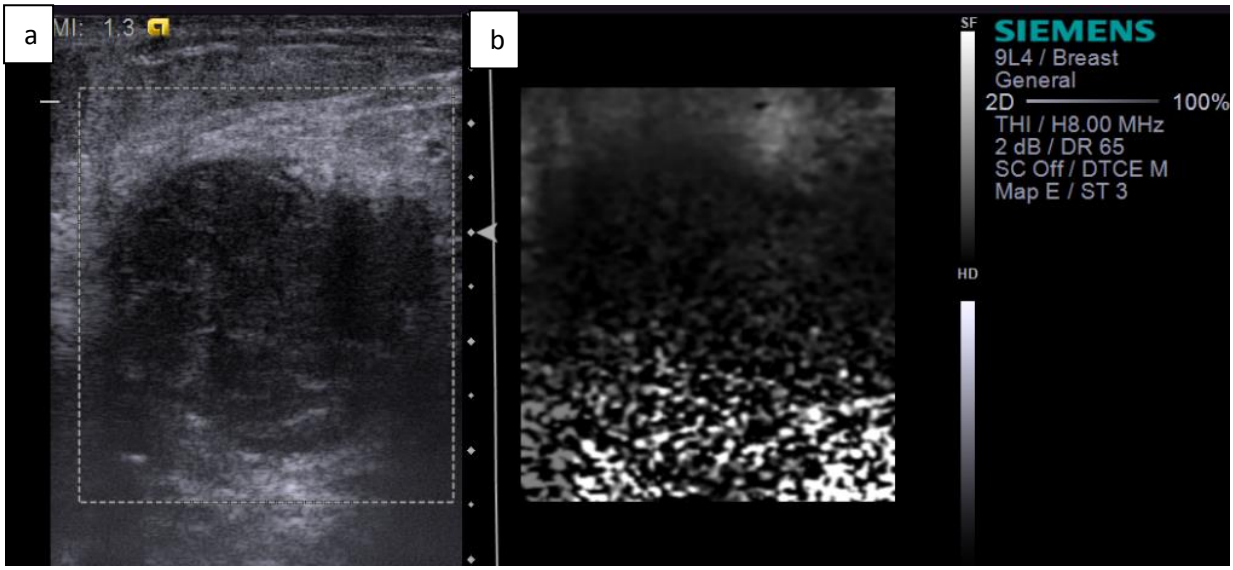


Figure 19: a) B-mode image showing an irregular hypoechoic mass. b) VTI image showing a mixed pattern of black and white areas. This lesion was found to be an invasive ductal carcinoma at biopsy.

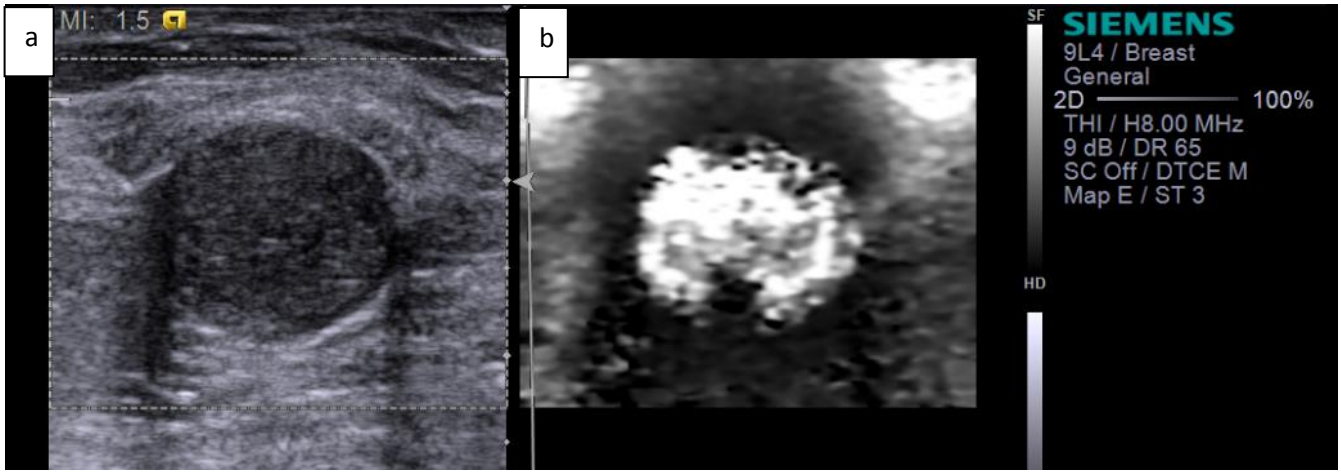


Figure 20: a) B-mode image showing a well-defined hypoechoic lesion with posterior acoustic enhancement. b) VTI image showing a white pattern indicative of no strain within the lesion. This lesion was found to have 'benign epithelial cells' on fine needle aspiration cytology.

2) Area Ratio:

There was significant difference in the area ratios between the two groups (p value <0.001). Values shown in table 5 and displayed as box plots in figure 19.

Mean area ratio (B-mode / VTI)		
Benign	Malignant	P value
1.33±0.82	0.38±0.49	<0.001

Table 5: Mean area ratio of benign and malignant lesions.

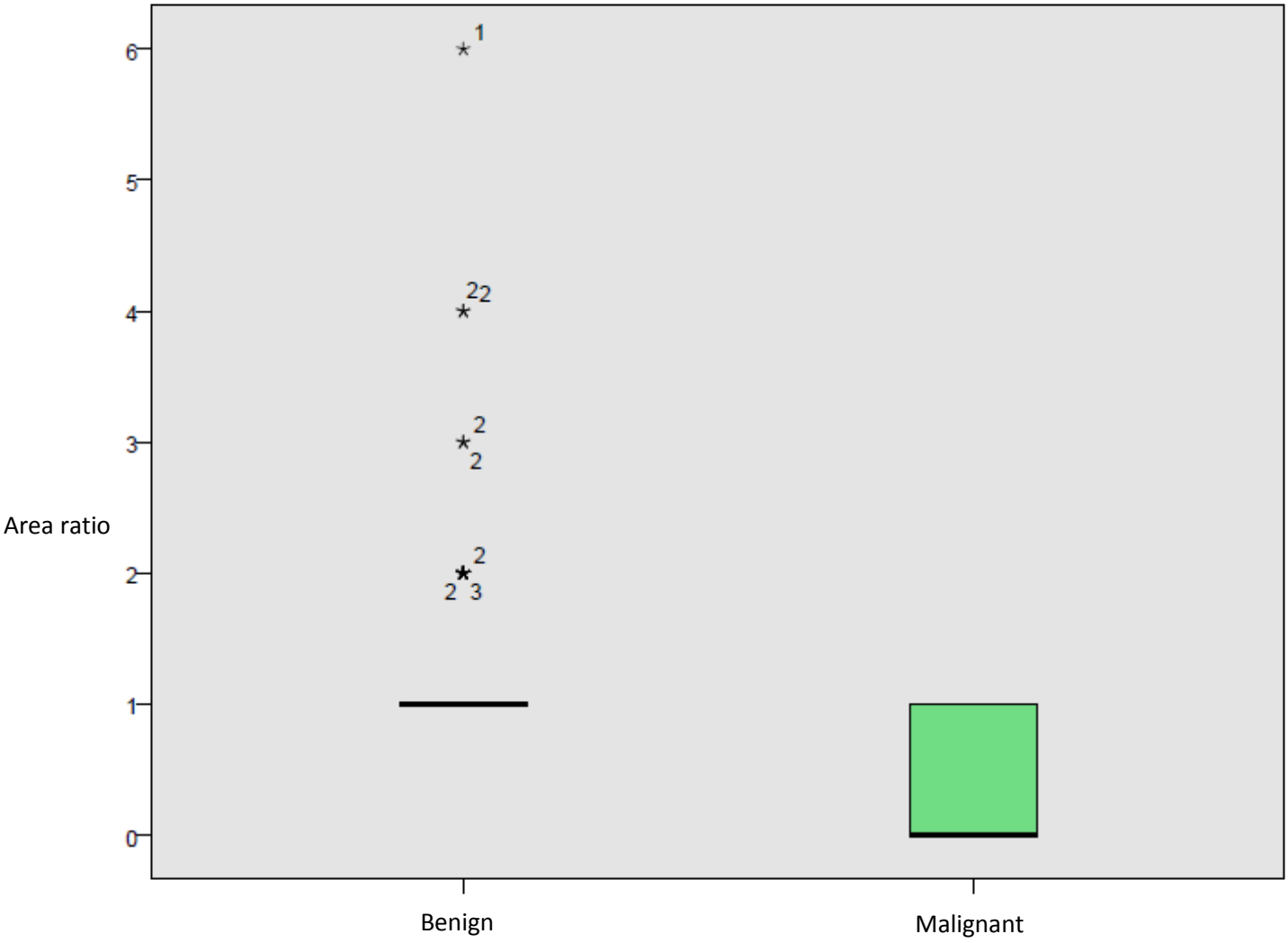


Figure 21: Box plot diagram showing the area ratio of the lesions within the benign and malignant group. The outliers are marked as circles and stars with the numbers indicating the elasticity scores on VTI. All the outliers in the benign group had ‘benign’ elasticity scores on VTI.

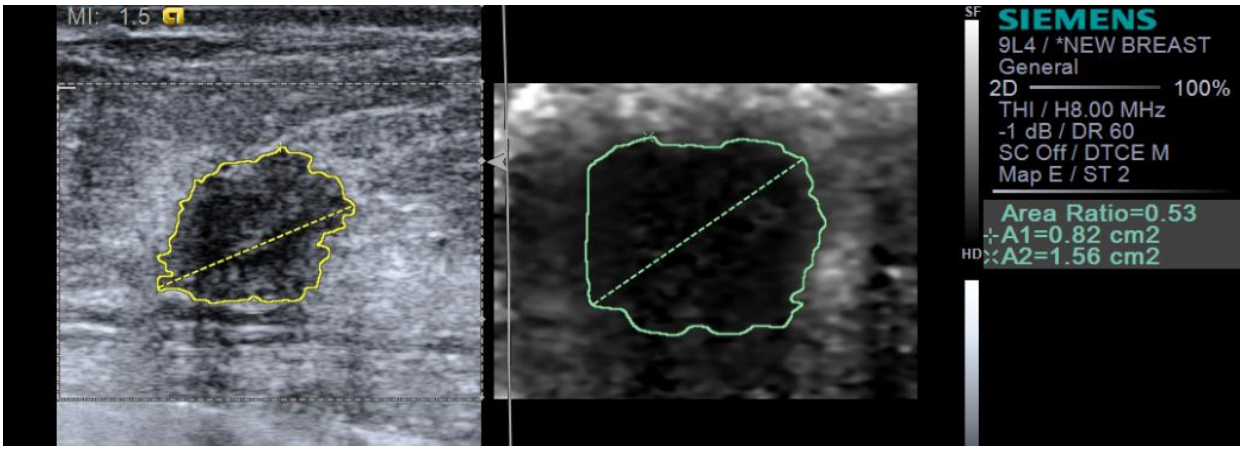


Figure 22: Invasive ductal carcinoma – Area larger and darker on the corresponding VTI image. Area Ratio of 0.53.

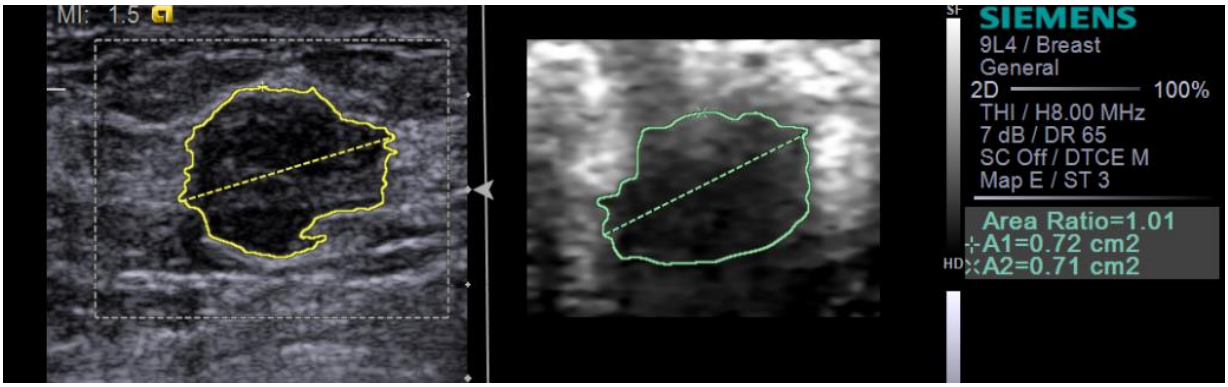


Figure 21: Fibroadenoma – Area appears similar on the corresponding VTI image. Area Ratio of 1.01.

3) Clinical palpation and VTI:

There was significant correlation between clinical palpation findings and VTI scoring (Chi square = 89.77, p value <0.001, df = 4).

The combined VTI scoring using score 1 to 3 as benign and score 4 to 5 as malignant also showed significant correlation with clinical palpation (Chi square = 86.15, p value <0.001, df = 1). Refer table 6&7.

Clinical palpation	VTI				
	1	2	3	4	5
Hard	---	---	3	2	29
Soft	20	77	27	3	14

Table 6: Clinical palpation and VTI elasticity scores on ARFI

Clinical palpation	VTI combined	
	Score 1-3	Score 4-5
Hard	8.8% (n=3)	91.3% (n=31)
Soft	87.9% (n=124)	12.1% (n=17)

Table 7: Clinical palpation and combined VTI (score 1-3 as benign and 4-5 as malignant) scores on ARFI:

4) Shape and VTI:

There was significant correlation between the shape of lesion on B-mode USG and the VTI scoring (Chi square = 65.48, p value<0.001, df = 8).

The combined VTI scoring using score 1 to 3 as benign and score 4 to 5 as malignant also showed significant correlation with the shape of the lesion (Chi square = 61.41, p value <0.001, df = 2). Refer table 8 & 9.

107 lesions out of 118 lesions (90.7%) with oval shape had benign scoring on VTI while 35 lesions out of 52 (67.3%) with irregular shape had malignant scoring on VTI.

Shape	VTI				
	1	2	3	4	5
Oval	16.1% (n=19)	54.2%(n=64)	20.3%(n=24)	1.7%(n=2)	7.6%(n=9)
Round	-	57.1%(n=4)	14.3%(n=1)	-	28.6%(n=2)
Irregular	1.9%(n=1)	17.3%(n=9)	13.5%(n=7)	5.8%(n=3)	61.5%(n=32)

Table 8: Shape descriptor of the lesion on B-mode USG and VTI elasticity scores on ARFI.

shape	VTI combined	
	Score 1-3	Score 4-5
Oval	90.7% (n=107)	9.3% (n=11)
Round	71.4% (n=5)	28.6% (n=2)
irregular	32.7%(n=17)	67.3%(n=35)

Table 9: Shape descriptor on B-mode USG and combined VTI elasticity scores on ARFI

5) Margin and VTI:

There was significant correlation between the margin of lesion on B-mode USG and the VTI scoring (Chi square = 100, p value<0.001, df = 16).

The combined VTI scoring using score 1 to 3 as benign and score 4 to 5 as malignant also showed significant correlation with the margin of the lesion (Chi square = 76.11, p value <0.001, df = 4). Refer table 10 &11

101 lesions out of 107 lesions (94.4%) with well-circumscribed margins had benign scoring on VTI while 12 lesions out of 14 (85.7%) with spiculated margins on B-mode also had malignant scoring on VTI.

Margin	VTI				
	1	2	3	4	5
Well-circumscribed	15.9%(n=17)	61.7%(n=66)	16.8%(n=18)	0.9%(n=1)	4.7%(n=5)
Microlobulated	5.3% (n=2)	21.1% (n=8)	28.9% (n=11)	10.5%(n=4)	34.2%(n=13)
Indistinct	-	8.3% (n=1)	8.3% (n=1)	-	83.3% (n=10)
Macrolobulated	16.7% (n=1)	16.7% (n=1)	16.7% (n=1)	-	50% (n=3)
Spiculated	-	7.1%(n=1)	7.1%(n=1)	-	85.7%(n=12)

Table 10: Margin descriptor on B-mode USG and VTI elasticity scoring on ARFI.

Margin	VTI combined	
	Score 1-3	Score 4-5
Well-circumscribed	94.4% (n=101)	5.6%(n=6)
Microlobulated	55.3% (n=21)	44.4%(n=17)
Indistinct	16.7% (n=2)	83.3% (n=10)
Macrolobulated	50% (n=3)	50% (n=3)
Spiculated	14.3%(n=2)	85.7%(n=12)

Table 11: Margin descriptor on B-mode USG and combined VTI scoring on ARFI

6) Orientation and VTI:

There was significant correlation between the orientation of the lesion on B-mode USG and the VTI scoring (Chi square = 42.62, p value<0.001, df = 4).

The combined VTI scoring using score 1 to 3 as benign and score 4 to 5 as malignant also showed significant correlation with the orientation of the lesion (Chi square = 41.69, p value <0.001, df = 1). Refer table 12 & 13.

122 lesions out of 148 lesions (82.4%) with parallel orientation had benign scoring on VTI while 22 lesions out of 29 (75.9%) with anti-parallel orientation on B-mode had malignant scoring on VTI.

Orientation	VTI				
	1	2	3	4	5
Parallel	13.5% (n=20)	49.3% (n=73)	19.6% (n=29)	2%(n=3)	15.5%(n=23)
Anti-parallel	-	13.8% (n=4)	10.3% (n=3)	6.9%(n=2)	69%(n=20)

Table 12: Orientation descriptor of lesion on B-mode USG and VTI elasticity scoring on ARFI

Orientation	VTI combined	
	Score 1-3	Score 4-5
Parallel	82.4% (n=122)	17.6% (n=26)
Anti-parallel	24.1% (n=7)	75.9% (n=22)

Table 13: Orientation descriptor of lesion on B-mode USG and combined VTI elasticity scoring on ARFI

7) Boundary and VTI:

There was significant correlation between the boundary of the lesion on B-mode USG and the VTI scoring (Chi square = 85.37, p value<0.001, df = 4).

The combined VTI scoring using score 1 to 3 as benign and score 4 to 5 as malignant similarly showed significant correlation with the boundary of the lesion (Chi square = 76.89, p value <0.001, df = 1). Refer table 14 & 15.

121lesions out of 136 lesions (89%) with abrupt interface on B-mode USG had benign scoring on VTI while 33 lesions out of 41 (80.5%) with echogenic halo on B-mode had malignant scoring on VTI.

Boundary	VTI				
	1	2	3	4	5
Abrupt interface	14.7% (n=20)	55.9% (n=76)	18.4% (n=25)	2.2%(n=3)	8.8%(n=12)
Echogenic halo	-	2.4% (n=1)	17.1% (n=7)	4.9%(n=2)	75.6%(n=31)

Table 14: Boundary descriptor of lesion on B-mode USG and VTI elasticity scoring on ARFI

Boundary	VTI combined	
	Score 1-3	Score 4-5
Abrupt interface	89% (n=121)	11% (n=15)
Echogenic halo	19.8% (n=8)	80.5% (n=33)

Table 15: Boundary descriptor of lesion on B-mode USG and combined VTI elasticity scoring on ARFI

8) Echopattern and VTI:

There was no significant correlation between the echopattern on B-mode USG and the VTI scoring (Chi square = 12.07, p value = 0.440, df = 12).

The combined VTI scoring using score 1 to 3 as benign and score 4 to 5 as malignant also showed no significant correlation with the echopattern (Chi square = 3.89, p value = 0.274, df = 3). Refer table 16 & 17.

Echopattern	VTI				
	1	2	3	4	5
Hyperechoic	50% (n=2)	25% (n=1)	25% (n=1)	-	-
Isoechoic	33.3% (n=1)	33.3% (n=1)	33.3% (n=1)	-	-
Hypoechoic	10.1% (n=16)	44.3% (n=70)	18.4% (n=29)	2.5% (n=4)	24.7% (n=39)
Complex	8.3% (n=1)	41.7% (n=5)	8.3% (n=1)	8.3% (n=1)	33.3% (n=4)

Table 16: Echopattern descriptor on B-mode USG and VTI elasticity scores on ARFI

Echopattern	VTI combined	
	Score 1-3	Score 4-5
Hyperechoic	100% (n=4)	-
Isoechoic	100% (n=3)	-
Hypoechoic	72.8% (n=115)	27.2% (n=43)
Complex	58.3% (n=7)	41.7% (n=5)

Table 17: Echopattern descriptor on B-mode USG and combined VTI scores on ARFI

9) Posterior acoustic features and VTI:

There was significant correlation between the posterior acoustic features on B-mode USG and the VTI scoring (Chi square = 24.34, p value <0.001, df = 4).

The combined VTI scoring using score 1 to 3 as benign and score 4 to 5 as malignant similarly showed significant correlation with the posterior acoustic features (Chi square = 23.35, p value <0.001, df = 1). Refer table 18 & 19.

Posterior acoustic features	VTI				
	1	2	3	4	5
Enhancement	12.7% (n=20)	46.8% (n=74)	19% (n=30)	2.5% (n=4)	19% (n=30)
Shadowing	-	15.8% (n=3)	10.5% (n=2)	5.3% (n=1)	68.4% (n=13)

Table 18: Posterior acoustic feature on B-mode USG and VTI scores on ARFI

Posterior acoustic features	VTI combined	
	Score 1-3	Score 4-5
Enhancement	78.5% (n=124)	21.5% (n=34)
Shadowing	26.3% (n=5)	73.7% (n=14)

Table 19: Posterior acoustic features on B-mode USG and combined VTI scores on ARFI

10) Calcification and VTI:

There was significant correlation between the presence or absence of calcification on B-mode USG and the VTI scoring (Chi square = 16.49, p value <0.05, df = 8).

The combined VTI scoring using score 1 to 3 as benign and score 4 to 5 as malignant also showed similar correlation with the calcification features (Chi square = 8.9, p value <0.05, df = 2). Refer table 20 & 21.

Calcification	VTI				
	1	2	3	4	5
Macrocalcification	6.2% (n=1)	37.5% (n=6)	43.8% (n=7)	-	12.5% (n=2)
Absent	11.8%(n=18)	45.4%(n=69)	14.4% (n=25)	2.6% (n=4)	23.7% (n=36)
Microcalcification	11.1% (n=1)	22.2% (n=2)	-	11.1% (n=1)	55.6% (n=5)

Table 20: Calcification on B-mode USG and VTI scores on ARFI

Calcification	VTI combined	
	Score 1-3	Score 4-5
Macrocalcification	87.5% (n=14)	12.5% (n=2)

Absent	73.7% (n=112)	26.3% (n=40)
Microcalcification	33.3% (n=3)	66.7% (n=6)

Table 21: Calcification on B-mode USG and combined VTI scores on ARFI

11) BIRADS category on B-mode USG and VTI:

There was significant correlation between the BIRADS category assigned by B-mode USG and the VTI scoring (Chi square = 107.41, p value <0.001, df = 16).

The combined VTI scoring using score 1 to 3 as benign and score 4 to 5 as malignant also showed similar correlation with the B-mode USG BIRADS category features (Chi square = 92.17, p value <0.001, df = 4). Refer table 22 & 23.

There were 16 lesions assigned as BIRADS 4a (low suspicion for malignancy) on B-mode which were assigned in the benign category (score of 1 to 3) on VTI. 6 lesions under BIRADS 3 category were called malignant on VTI (score 4 and 5), while 2 BIRADS 5 lesions were called benign on VTI.

BIRADS category	VTI				
	1	2	3	4	5
BIRADS 3	15.8% (n=15)	62.1% (n=59)	15.8% (n=15)	1.1% (n=1)	5.3% (n=5)
BIRADS 4a	17.6% (n=3)	41.2% (n=7)	35.3% (n=6)	-	5.9% (n=1)
BIRADS 4b	9.1% (n=2)	31.8% (n=7)	31.8% (n=7)	4.5% (n=1)	22.7% (n=5)
BIRADS 4c	-	16.7% (n=3)	16.7% (n=3)	11.1% (n=2)	55.6%(n=10)
BIRADS 5	-	4% (n=1)	4% (n=1)	4% (n=1)	88% (n=22)

Table 22: BIRADS category on B-mode USG and VTI scores on ARFI

BIRADS category	VTI combined	
	Score 1-3	Score 4-5
BIRADS 3	93.7% (n=89)	6.3% (n=6)
BIRADS 4a	94.1% (n=16)	5.9% (n=1)
BIRADS 4b	72.7% (n=16)	27.3% (n=6)
BIRADS 4c	33.3% (n=6)	66.7% (n=12)
BIRADS 5	8% (n=2)	92% (n=23)

Table 23: BIRADS category on B-mode USG and combined VTI scores on ARFI

VTQ findings:

1) Lesion SWV:

The mean SWV of the benign group was 3.08 ± 1.99 m/s while that for the malignant group was 8.43± 1.75m/s (p value <0.001).

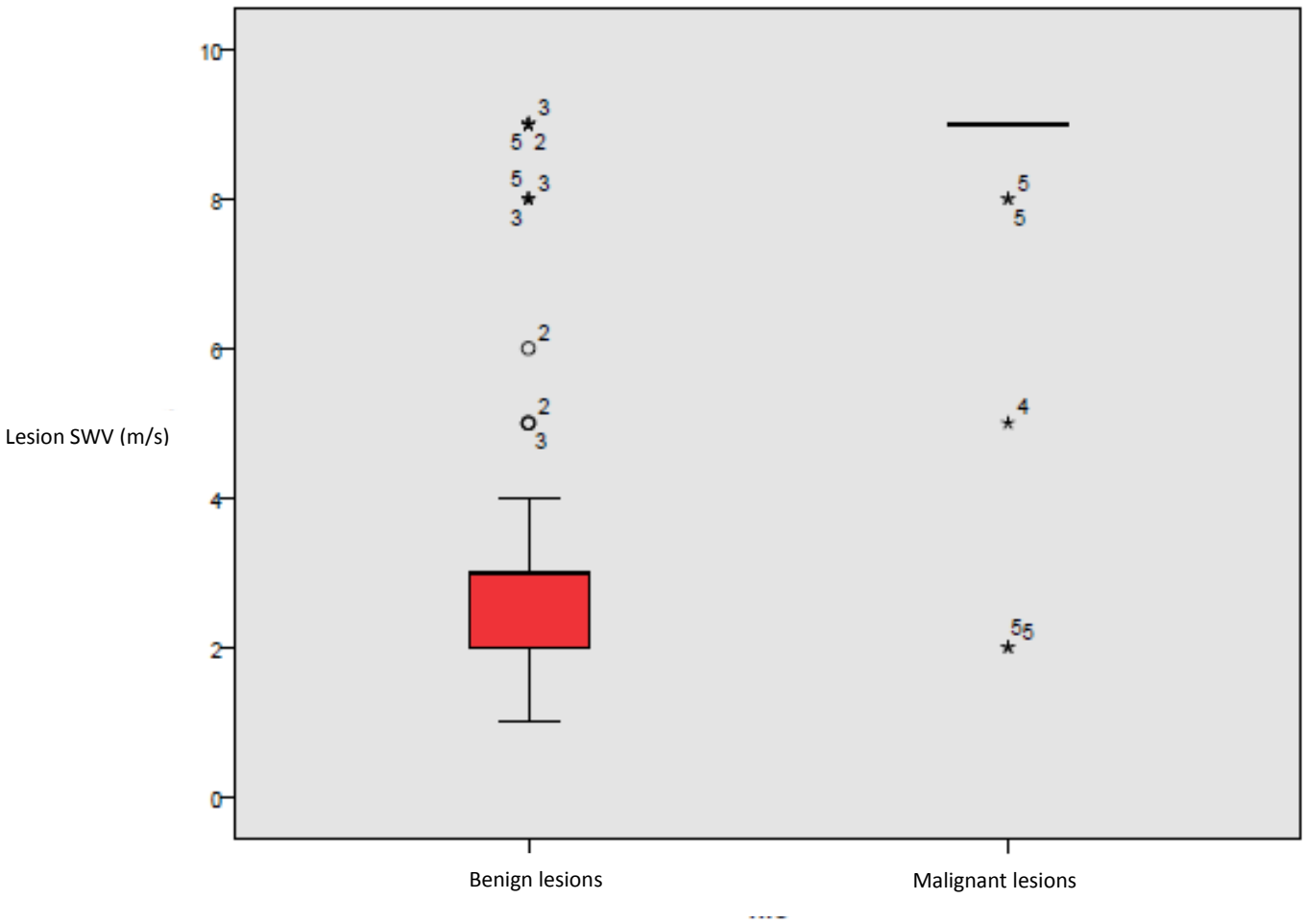


Figure 23: Box plot diagram showing SWV values for benign and malignant lesions. The boxes indicate the lower to upper quartiles (25-75th percentiles). The outliers are indicated by circles and stars with the numbers indicating the VTI elasticity scores. The 5 outliers in the malignant group were correctly scored as 'malignant' (score of 4 and 5) by VTI. 7 outliers in the benign group were correctly categorized as benign (score of 2 and 3) by VTI.

2) SWV ratio:

The mean SWV ratio between the lesion and surrounding reference tissue was 2.03±1.1 for the benign group while it was 3.77±1.98 for the malignant group (p value <0.001).

Feature	Benign (n=95)	Malignant (n=35)	P value
Lesion SWV, m/s	3.08 ± 1.99	8.43± 1.75	<0.001
SWV ratio	2.03±1.1	3.77±1.98	<0.001

Table 24: mean Shear Wave Velocity (SWV) within the lesion (m/s) and SWV ratio in the benign and malignant group.

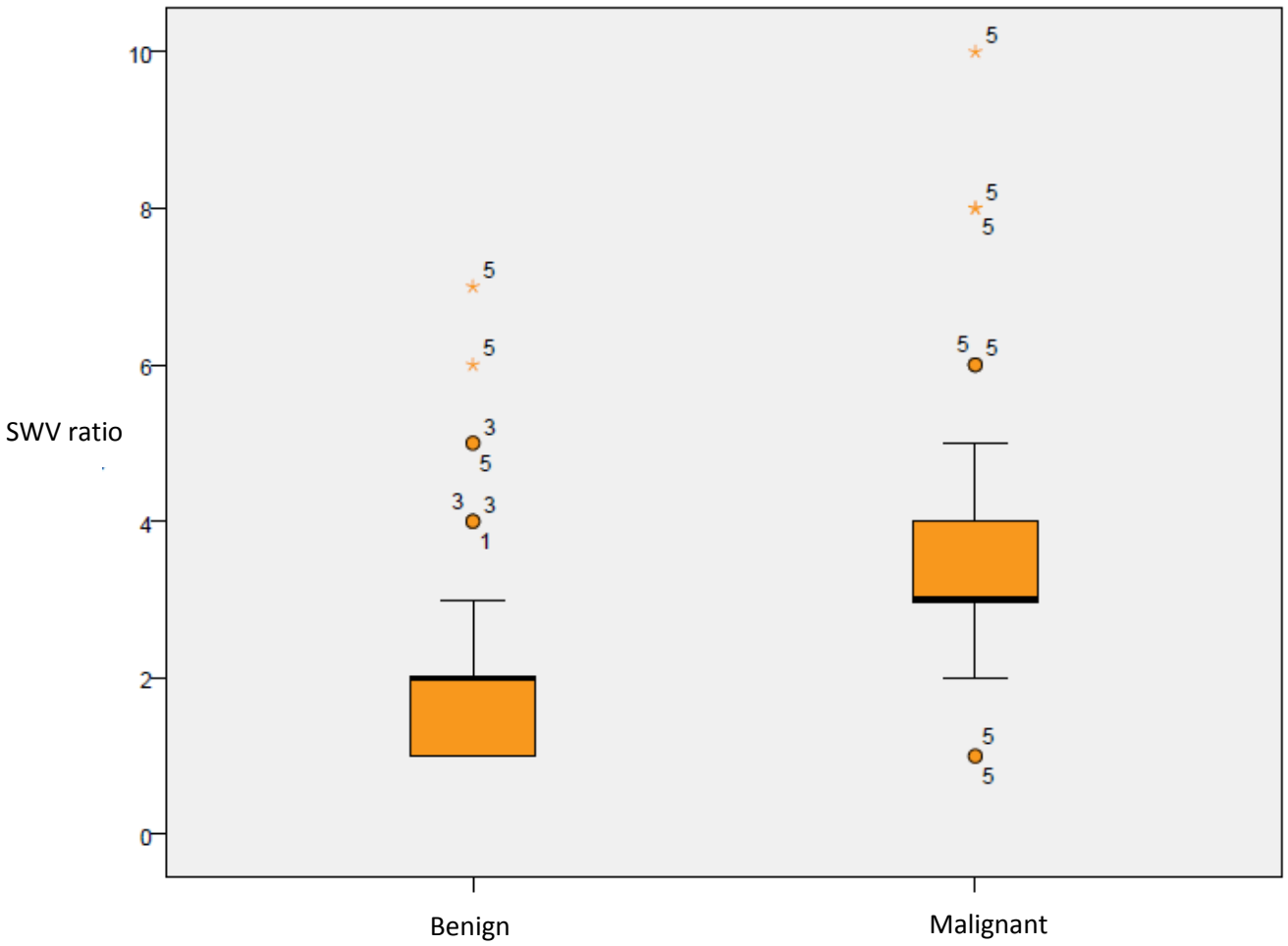


Figure 24: Box plot diagram showing the SWV ratio of the benign and malignant group. The outliers are marked as circles and stars with numbers indicating the VTI elasticity scores. All the 7 malignant lesions and 4 out of 7 benign lesions marked as outliers in the box plots show correct categorization by VTI elasticity scores.

Diagnostic performance of B-mode BIRADS, VTI, VTQ:

1) Performance of B-mode USG:

The sensitivity, specificity, PPV, NPV and accuracy of B-mode USG was 91.4%, 91.5%, 80%, 96.6% and 91% respectively.

ROC curve drawn for B-mode USG showed area under the curve (AUC) of 0.948 indicating good performance.

2) Performance of VTI:

a) Elasticity score:

Combining the elasticity scores of 1 to 3 as benign and scores of 4 and 5 as malignant, the AUC, sensitivity, specificity, PPV, NPV and accuracy of VTI using elasticity scores was 0.981, 100%, 92.6%, 83.3%, 100% and 94.6% respectively.

b) Area Ratio:

Using the optimal cut off value of 1.41 for area ratio, the calculated AUC, sensitivity, specificity, PPV, NPV and accuracy was 0.86, 76%, 92.5%, 76%, 92.5% and 72.3% respectively.

3) Performance of VTQ:

Analysis of the ROC curve for lesion SWVs in differentiating malignant and benign masses gave the best cut-off point at 5.5m/s with sensitivity, specificity, positive predictive value, negative predictive value, accuracy of 91.4%, 89.4%,76.1%, 96.5%, 90% respectively (figure 24).

Decreasing the cut-off point to 4.5m/s did not improve the specificity while marginally improving the sensitivity (sensitivity 94.2% and specificity 86.3%).

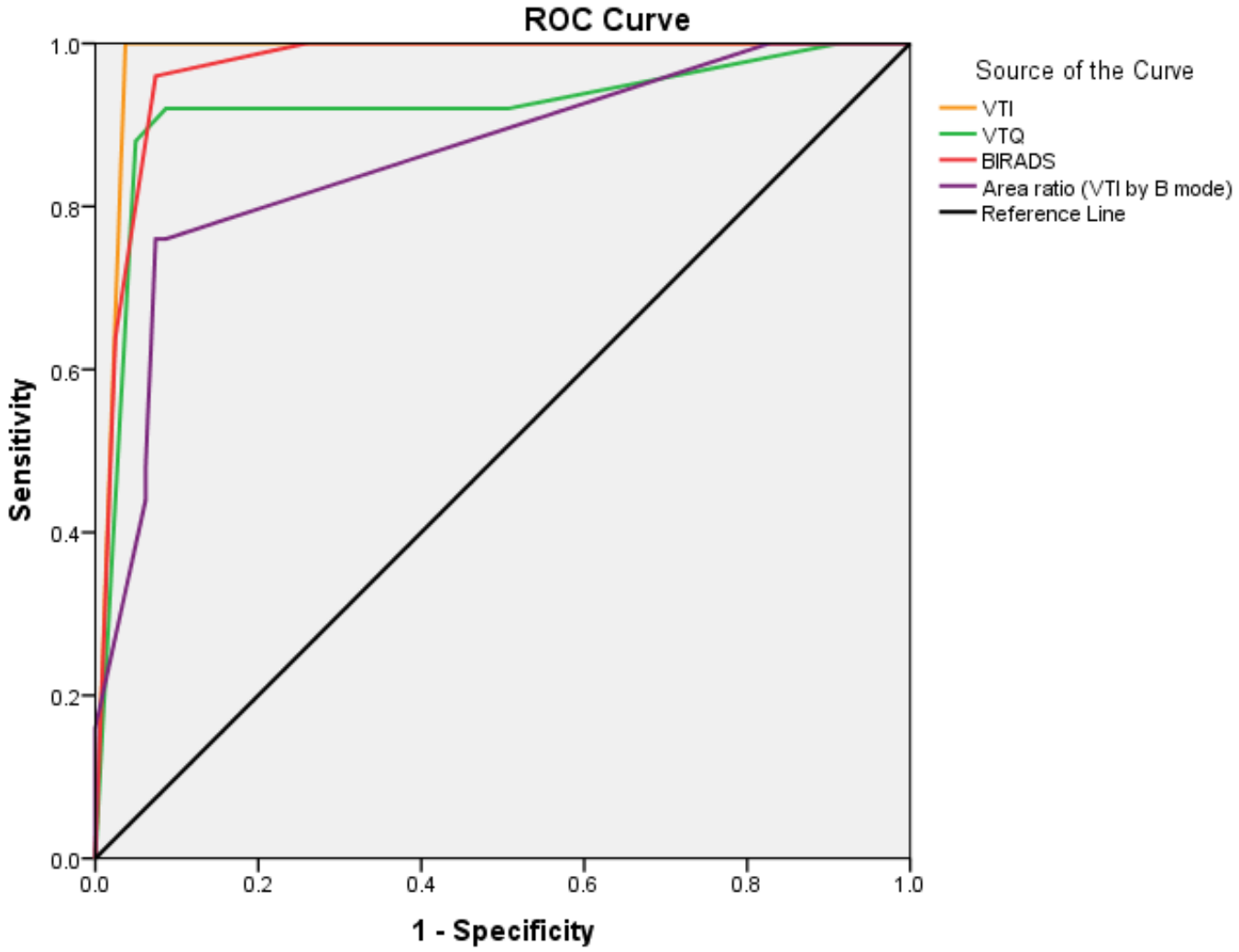


Figure 25: ROC curve showing the area under curve for VTI (elasticity score), VTQ (SWV), BIRADS, and VTI (area ratio).

Diagnostic performance of combined VTI+VTQ, B-mode BIRADS + VTI, B-mode BIRADS + VTQ and B-mode BIRADS+ VTI+VTQ:

1) Performance of VTI (elasticity score) + VTQ:

The combined performance of VTI (elasticity score) and VTQ yielded AUC, sensitivity, specificity, PPV, NPV and accuracy of 0.941, 91.4%, 96.8%, 91.4%, 96.8% and 95.3% respectively. An elasticity score of ≥ 4 and cut off SWV value >5.5m/s was used for predicting malignancy.

2) Combined performance of B-mode BIRADS + VTI (elasticity score):

The performance of combined BIRADS B-mode USG and VTI was evaluated assuming malignancy if either was positive (BIRADS 4a, 4b, 4c and 5 on B-mode and elasticity score of ≥4 taken as positive). The resultant AUC, sensitivity, specificity, PPV, NPV and accuracy were 0.952, 91.4%, 98.9%, 96.9%, 96.9% and 96.9% respectively.

This combination was found to have the second highest specificity and accuracy when compared with the other combinations.

3) Combined performance of B-mode BIRADS + VTQ:

The performance of combined BIRADS B-mode USG and VTQ was evaluated assuming malignancy if either were positive (BIRADS 4a, 4b, 4c and 5 on B-mode and cut off SWV value >5.5m/s taken as positive). The resultant AUC, sensitivity, specificity, PPV, NPV and accuracy were 0.913, 85.7%, 96.8%, 90.9%, 94.8% and 93.8% respectively.

4) Combined performance of B-mode BIRADS + VTI + VTQ:

The combined performance of all three modalities in predicting malignancy was evaluated with the above mentioned cut off values. The resultant AUC, sensitivity, specificity, PPV, NPV and accuracy were 0.929, 85.7%, 100%, 100%, 95% and 96% respectively.

This combination had the highest sensitivity, specificity and overall accuracy.

5) Combined performance of B-mode BIRADS + Area Ratio:

Using a cut off value of >1.41 for area ratio, the sensitivity, specificity, PPV, NPV and accuracy were 51.4%, 100%, 100%, 84.8% and 86.9% respectively.

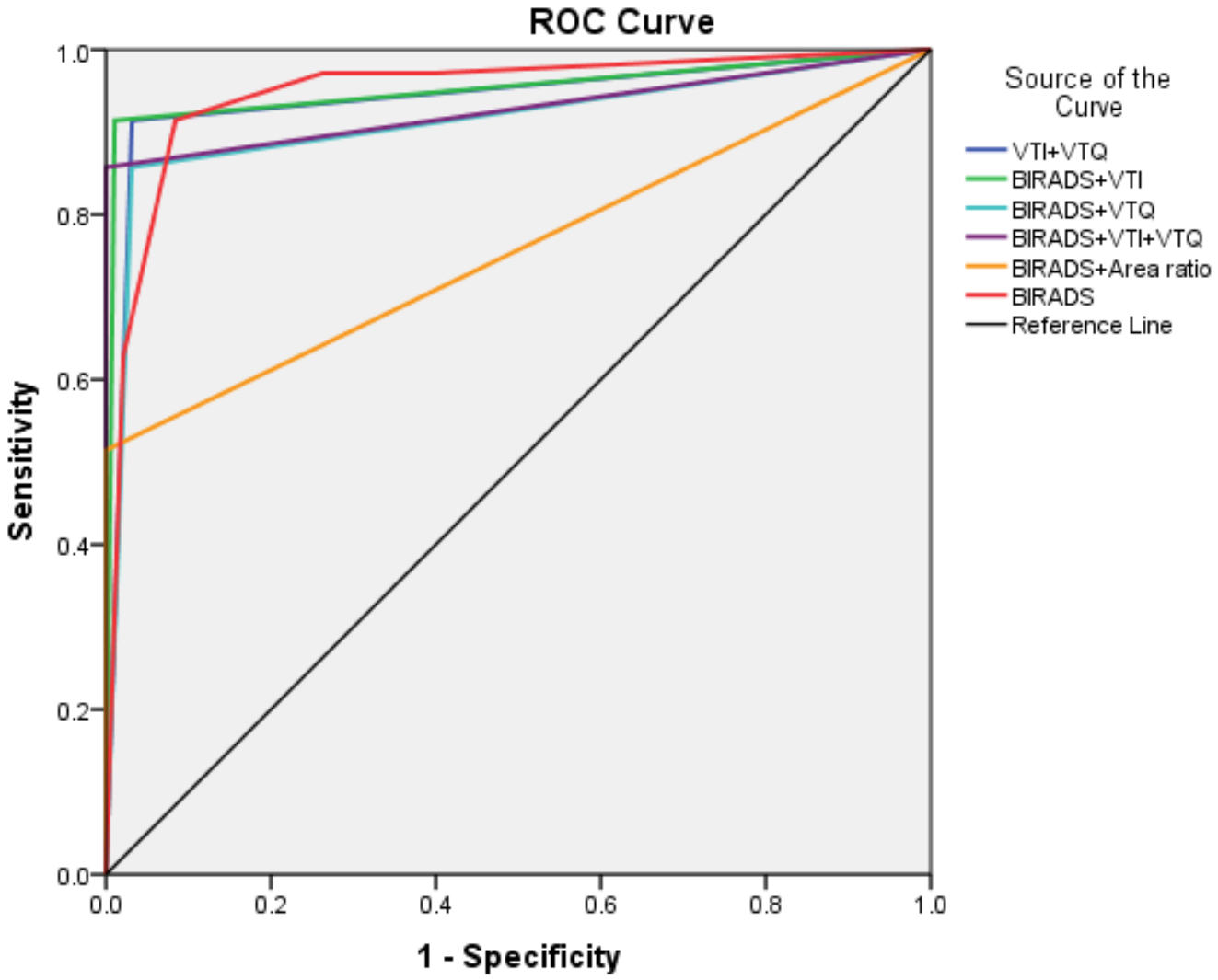


Figure 26: ROC curve showing the area under curve for BIRADS, VTI, VTQ, VTI+VTQ, BIRADS + VTI and BIRADS +VTQ.

	Area under the curve	Sensitivity	Specificity	PPV	NPV	Accuracy
B-mode BIRADS	0.948	91.43	91.58	80	96.67	91.5
VTI elasticity score	0.981	100	92.6	83.3	100	94.6
VTQ (lesion SWV)	0.919	91.4	89.4	76.1	96.5	90
Area ratio (VTI area/B-mode area)	0.86	76	92.5	76	92.5	72.3
VTI+VTQ	0.941	91.4	96.8	91.4	96.84	95.3
B-mode BIRADS+VTI	0.952	91.43	98.95	96.97	96.9	96.9
B-mode BIRADS+VTQ	0.913	85.7	96.8	90.9	94.8	93.84
B-mode BIRADS+VTI+VTQ	0.929	85.7	100	100	95	96
B-mode BIRADS+Area ratio	0.757	51.4	100	100	84.8	86.9

Table 25: performance of B-mode BIRADS, VTI, VTQ, area ratio (VTI/B-mode), combined B-mode + VTI, combined B-mode + VTQ and combined B-mode + area ratio in differentiating benign and malignant lesions in a total of 130 solid breast lesions using cut off values of 5.5m/s for lesion SWV on VTQ and area ratio of 1.41 on VTI.

DISCUSSION

The use of sonographic BIRADS lexicon in the assessment of breast lesions has substantially brought uniformity in reporting breast lesions. However, there are still situations where benign and malignant features on ultrasound can overlap giving rise to indeterminate lesions. Also, subjective factors arising from the reporting person can affect the final assessment category.

Elastography is based on measurement of tissue stiffness, the information obtained being either qualitative in the form of visual assessment of strain patterns or quantitative in the form of length / area ratio calculations and shear wave velocity measurements. Recent growing interest in the application of elastography for breast imaging has resulted in refinement of the technology and development of several methods for measuring tissue stiffness. ARFI is a relatively new technology which has the advantage of being operator independent because unlike the conventional strain elastography techniques where manual compression is required, ARFI does not require manual compression.

A literature search on studies using ARFI elastography on breast lesions in Indian population showed that the diagnostic utility of ARFI has not been performed in our Indian population.

In this study, we evaluated the diagnostic performance of both the qualitative and quantitative parameters (VTI and VTQ) of ARFI elastography using histopathology as the reference standard.

Elasticity scores on VTI were used as qualitative parameters while Area Ratio on VTI, lesion Shear wave velocity and shear wave velocity ratio were used as quantitative parameters for assessing the stiffness characteristics of the lesions. We also performed a comparative analysis of the diagnostic performances of B-mode USG BIRADS, VTI and VTQ alone as well as the performance of combined VTI and VTQ, combined B-mode USG with VTI and combined B-mode USG with VTQ.

B-mode USG using BIRADS lexicon:

B-mode USG using BIRADS for lesion characterization showed a good performance with sensitivity, specificity, PPV, NPV and accuracy of 91.4%, 91.5%, 80%, 96.6% and 91.5% respectively.

VTI imaging:

In our study, VTI using elasticity scores was found to have the maximum area under the curve (AUC=0.981) thus indicating a high diagnostic performance in predicting malignancy.

To compare the performance of VTI and B-mode USG BIRADS, VTI scores were subdivided into 'benign'(score of 1 to 3) and 'malignant' (score of 4 and 5) groups while 'benign' group in B-mode USG signified a BIRADS score of 3 and 'malignant' group included the BIRADS category 4 and 5 lesions.

The VTI variables found to be significantly different between the benign and malignant groups were:

1) Elasticity scores (p value <0.001)
2) Area Ratio (B-mode / VTI) (p value <0.001)

A significant difference was observed between the elasticity scores of the benign and malignant lesions (p<0.001). This finding is in agreement with the results of prior studies which have used the 5 point scoring system (24,30,40,42).

All the 35 malignant lesions had an elasticity score of 4 or 5 on VTI and were correctly classified as ‘malignant’.

The optimal cut off for elasticity score to differentiate between the benign and malignant group in our study was a score of 4 and above. This cut off point yielded sensitivity, specificity, PPV, NPV and accuracy of 100%, 92.6%, 83.3%, 100% and 94.6% respectively.

The area ratio (B-mode / VTI) also showed a significant difference between the benign and malignant group (1.33±0.82 for benign lesions vs 0.38±0.49 for malignant lesions, p value <0.001).

Using a cut-off value of 1.41 to predict malignancy, the AUC, sensitivity, specificity, PPV, NPV and accuracy was 0.86, 76%, 92.5%, 76%, 72.3% respectively.

Elastography using VTI elasticity scores (ES) – comparison with prior studies:

Author	Total	Bng	Mlg	Mean ES (Bng)	Mean ES (Mlg)	Cut off score	Sen (%)	Sp (%)
Itoh et al, 2006	111	59	52	2.1±1.0	4.2±0.9	Between 3 & 4	86.5	89.8
Kim et al, 2014	157	40	117	1.6±0.8	3.7±1	Between 2 & 3	77.5	93.2
Our study	130	95	35			Between 3&4	100	92.6

We found good correlation between VTI and findings on clinical palpation (p value <0.001) as well as with the following B-mode USG features:

1) Shape
2) Margin
3) Orientation
4) Boundary
5) Posterior acoustic features
6) Calcification

There was no significant correlation between the VTI scores and echopattern on B-mode USG.

We also found good correlation between the final BIRADS category assigned by B-mode USG and VTI elasticity scores (p value <0.001)

VTQ imaging:

There was a significant difference in the mean shear wave velocity between the benign and malignant lesions (3.08 ± 1.99 m/s for benign and 8.43± 1.75m/s for malignant group, p value <0.001). This finding is also concordant with the other studies(37,38,42–44,47).

In our study, using a cut off mean SWV value of 5.5m/s to predict malignancy, we found a sensitivity, specificity, PPV, NPV and accuracy of 91.4%, 89.4%, 76.1%, 96.5% and 90% respectively. This result indicates that SWV can be used for ruling out malignancy, i.e. the presence of malignancy can be reliably detected by SWV measurement.

In the evaluation of SWV ratios between the benign and malignant lesions, we found significant increase in SWV ratios in the malignant group (2.03±1.1 for the benign group and 3.77±1.98 for the malignant group, p value <0.001).This is also in agreement with the results from previous studies(38).

In our study, a repeated measurement of 'X.XX' was taken as 9.0m/s (in the absence of calcification) which is the maximum limit measurable by the machine. Two reasons have been proposed to explain the occurrence of this ‘X.XX’ reading, first reason being movement of the target creating signals which are not accepted by the quality assurance setting of the machine. The second reason is attributed to the presence of very hard tissue whose stiffness is beyond a value of 9.10m/s set in the machine (37).This result was seen in all the 35 malignant lesions in our series. Therefore we consider that a reading of 'X.XX' could be used as a reliable indicator of malignancy. One of the benign lesions which showed ‘X.XX’ reading was found to have extensive hyalinization on histopathological examination hence explaining the false positive result.

Elastography using VTQ shear wave velocity – comparison with prior studies:

Author	Total	Bng	Mlg	SWV (Bng)	SWV (Mlg)	Cut off (SWV)	Sen (%)	Sp (%)	Acc (%)
Kim et al, 2014 (42)	157	40	117	2.22±0.88	4.23±1.09	3.52	97.5	91.5	93
Zhou et al, 2013 (39)	175	108	67	2.68±1.2	5.62±3.26	4.19	55.2	95.8	70
Meng et al, 2011 (44)	92	65	27	3.25±2.03	8.22 ±1.27	-	-	-	-
Jin et al, 2012 (38)	122	66	56	2.44±1.27	5.74±1.68	3.65	89.3	80.3	-
Bai et al, 2012 (37)	143			2.25±0.59	5.96±2.96	3.06	75.6	95.1	85.6
Tozaki et al, 2012 (45)	161	18	43	-	-	3.59	91	93	92
Our study	130	95	35	3.08 ± 1.99	8.43± 1.75	5.5	91.4	89.4	90

Combination of modalities:

The combined use of VTI and VTQ showed good performance with sensitivity, specificity, PPV, NPV and accuracy of 91.4%, 96.8%, 91.4%, 96.8 and 95.3% respectively. Also, it was observed that combining B-mode USG and VTI showed similar sensitivity to the use of B-mode USG alone with an improved specificity from 91.5% (B-mode USG alone) to 98.9% (combination). On the other hand, combining B-mode USG and VTQ showed a reduction in the sensitivity while improving the specificity to 96.8%. Combination of the three modalities resulted in 100%

specificity and PPV with a lower sensitivity compared to B-mode alone. The combination of B-mode with area ratio of VTI resulted in 100% sensitivity and PPV however the sensitivity was reduced to 51.4%.

Modification of BIRADS category with elastography findings:

Using the cut off values obtained from ARFI elastography to modify the B-mode sonographic BIRADS category, we found that ARFI can help in decision-making regarding indeterminate lesions and ultimately reduce the number of biopsies. We observed that from a total of 95 benign lesions, 38 lesions were assigned as 'suspicious of malignancy' requiring tissue diagnosis. When we used VTI elasticity scores to modify the sonographic BIRADS category, 34 lesions from the 38 lesions could be downgraded from BIRADS 4 or 5 to BIRADS 3, implying that only 4 out of the 38 lesions required tissue diagnosis based on the modified BIRADS category. This amounted to approximately 40% biopsy rate among benign lesions using B-mode USG with a potential reduction to 4.2% biopsy rate if VTI elasticity scores were used to downgrade lesions.

LIMITATIONS

This study was subject to a few limitations:

1. The fixed size of the ROI box for SWV measurement limited its use in lesions smaller than 10mm. Also, strain elastography could not be used for large lesions exceeding the FOV.

2. Evaluation of the diagnostic performance based on the internal composition of the mass was not performed. For example, a large mass with necrosis can affect the velocity measurements and elasticity scoring. Also, benign masses with predominant fibrotic or hyalinised tissue would falsely give a high SWV measurement.

3. Assessment based on the histologic subgroups were not performed as the sample size in these subgroups especially the malignant group were small.

4. This study was done in the early learning curve period of a recently introduced breast imaging technique in our department.

5. Consideration of confounding factors such as breast thickness and depth of lesion were not done in the analysis.

CONCLUSIONS

In conclusion, ARFI elastography using both VTI and VTQ significantly increased the diagnostic performance in differentiating benign and malignant masses.

1. Combined criteria using B-mode USG BIRADS lexicon and VTI elasticity score had the best diagnostic performance, the performance being superior to the use of B-mode USG BIRADS and VTI alone.

2. Elasticity scores obtained by VTI was superior to VTQ in its diagnostic performance. VTI using elasticity scores had a negative predictive value of 100% in our series indicating that this test is highly reliable in excluding malignancy. However, our final malignant group was small and therefore, further studies with larger sample size may be required to validate this finding.

3. A cut-off shear wave velocity of 5.5m/s was most useful in identifying malignant breast masses. Our cut-off value is significantly higher compared to other studies (38,42). Further investigations are needed to examine association between shear wave velocity of breast lesions and population based factors like tumour receptor status, tumour stage at presentation etc.

4. We also found that using VTI to modify the sonographic BIRADS category could potentially downgrade indeterminate lesions and reduce the number of biopsies which would otherwise be performed on benign lesions.

We conclude that ARFI is a fairly simple, non-operator dependent technique which may be used as an adjunct modality with the existing B-mode ultrasound or mammography to improve characterization of lesions and thereby avoid unnecessary biopsy in lesions with low risk of malignancy.

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ANNEXURES

1. Proforma

A study on the role of Acoustic Radiation Force Imaging (ARFI) in differentiating benign and malignant lesions in patients with solid breast lesions

Serial no:

1. Hosp no: 2. Age:

Clinical information:

1. Clinical palpation: 1 - Hard 2 - Soft
2. Family history of breast cancer: 1 – yes 2 – no
3. Hormone replacement: 1 – yes 2 – no

Imaging findings: (based on ACR BIRADS US lexicon)

B-mode USG:

Size – mm

Shape –

1. Oval
2. Round
3. Irregular

Margin –

1. Circumscribed
2. Microlobulated
3. Indistinct
4. Angular
5. Spiculated

Orientation –

1. Parallel
2. Anti-parallel

Boundary –

1. Abrupt interface
2. Echogenic halo

Echopattern –

1. Hyperechoic
2. Isoechoic
3. Hypoechoic
4. Complex

Posterior acoustic features –

1. Enhancement
2. Shadowing

Calcification –

1. Macrocalcification
2. Absent
3. Microcalcification

BIRADS score

1. BIRADS 3
2. BIRADS 4a
3. BIRADS 4b
4. BIRADS 4c
5. BIRADS 5

ARFI elastography:

Area 1 (VTI) -

Area 2 (B-mode) -

Area Ratio -

SWV of Lesion (SWVL)

SWVL1	SWVL2	SWVL3	SWVL4	SWVL5

SWV of Surrounding tissue (SWV)

SWV1	SWV2	SWV3	SWV4	SWV5

Mean SWV ratio of lesion to surrounding tissue:

Histopathology:

1 – Benign

2 – Malignant

1. Benign	**2. Malignant**
1 Fibroadenoma	1. Invasive ductal ca
2 Adenosis	**2.** Invasive lobular ca
3 Inflammatory	3. Ductal ca in-situ
	4. Mucinous ca

Hormone receptor status:

ER	**PR**	**Her2Neu**
1 – positive	1 – negative	1 – negative
2 – negative	2 – positive	2 – positive

2. Consent form

INFORMATION SHEET FOR INFORMED CONSENT

Study Title: A study on the role of Acoustic Radiation Force Impulse (ARFI) imagingin differentiating benign and malignant breast lesions

You are requested to participate in a study to see if a new ultrasound technique called ARFI can help in predicting whether a lesion is benign or cancerous before you undergo biopsy. The final diagnosis will be given by microscopic examination of the tissue. By using this imaging technique we may be able to predict the nature of the lesion and avoid a biopsy.

What is ARFI? How does it differentiate benign from cancerous lesions?

ARFI is a type of ultrasound which can measure the hardness of tissues. It is known that cancerous tissues are harder than benign tissues and ARFI uses this stiffness information to predict whether a lesion is likely to be benign or cancerous.

Does ARFI have any side effects?

No, ARFI is comparable to the conventional ultrasound used in routine imaging.

There is no radiation exposure.

If you take part what will you have to do?

If you agree to participate in this study, you will have to come for ARFI study after your ultrasound. This study will take about 10-15minutes.

There will be no change in the other treatment and investigations which are advised by

your doctor.

No blood test will be required for this study.

Will you have to pay for the ARFI study?

No, you will not be charged for the ARFI study. All other investigations will continue in the usual manner as advised by your doctor.

What happens after the study is over?

You may or may not benefit immediately from this study since the final results of this study will interpreted at the end of 1 year. If we come to a conclusion that the study is beneficial, we will be able to use information in assessing patients with similar breast lesions in future.

Will your personal details be kept confidential?

The results of this study will be published in a medical journal but your identity will not be revealed in any manner. However, the images may be reviewed by other specialists associated with the study without your additional permission.

CONSENT TO TAKE PART IN STUDY

Study Title: A study on the role of Acoustic Radiation Force Impulse (ARFI) imaging in differentiating benign and malignant breast lesions

Study Number:

Participant's Name:

Age:

I.....son/daughter of.....

Declare the following: (please tick the boxes)

(i)I have read and understood the information sheet provided to me regarding this study and have had the opportunity to ask questions.

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

(iii) I understand that the study staff and the Ethics Committee will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).

(v) I agree to take part in the above study.

Signature (or Thumb impression) of participant:

Date: _____/_____/_____

Name: _____ Signature:

Signature of the Investigator: _____

Date: _____/_____/_____ Study Investigator's Name: _____

3. TNM staging of breast cancer

Primary tumor (T)

Tx – primary tumour cannot be assessed

T0 – no evidence of primary tumour

Tis – carcinoma in-situ

Tis (DCIS) – Ductal carcinoma in-situ

Tis (LCIS) – Lobular carcinoma in-situ

Tis (Pagets) – Paget's disease of the nipple

T1 – tumour less than 20mm in greatest dimension

mi - tumour less than 1mm in greatest dimension

a - tumour more than 1mm but less than 5mm

b - tumour more than 5mm but less than 10mm

c - tumour more than 10mm but less than 20mm

T2 - tumour more than 20mm but less than 50mm

T3 - tumour more than 50mm

T4 – any size tumour with direct extension to the chest wall + or - skin

a – extension to chest wall

b – ulceration and / or ipsilateral satellite nodules and / or edema

c – both a and b

d – inflammatory carcinoma

Regional lymph nodes (N)

Nx – cannot be assessed

N0 – no nodes

N1 – involvement of ipsilateral movable level I, II axillary nodes

N2 - involvement of ipsilateral fixed level I, II axillary nodes, clinically detected ipsilateral internal mammary nodes without clinically evident axillary nodes.

a - involvement of ipsilateral level I, II axillary nodes which are matted or stuck to other structures

b - metastatic involvement of clinically detected ipsilateral internal mammary nodes without clinically evidence t level I, II axillary nodes

N3 – metastatic involvement of ipsilateral infraclavicular level III axillary nodes +/- level I and II nodes or in clinically detected ipsilateral internal mammary nodes with level I and II nodes, or

metastases in ipsilateral supraclavicular node +/- axillary or internal mammary nodes.

a - ipsilateral infraclavicular nodes

b - ipsilateral axillary or internal mammary nodes

c - ipsilateral supraclavicular node

Distant metastases (M)

M0 – no clinicoradiologic evidence of distant metastases

cM0(i+) - no clinicoradiologic evidence of distant metastases, but molecularly or microscopically detected tumour cells that are <0.2mm in an asymptomatic patient

M1 – distant metastases